UNIVERSITÄT BONN

2nd Bonn Conference on Mathematical Life Sciences

Abstract Book

BONN CENTER FOR MATHEMATICAL LIFE SCIENCES

2nd Bonn Conference on Mathematical Life Sciences

March 16-19, 2026
Auditorium center Poppelsdorf

Abstract book

Version_20260312

Content

2nd Bonn Conference on Mathematical Life Sciences

Pocket programme

UNIVERSITÄT BONN — BONN CENTER FOR MATHEMATICAL LIFE SCIENCES

Monday, March 16, 2026

12:30 – 14:00 Registration & Coffee — *Foyer*

14:00 – 14:30 Welcome & Opening remarks — *Lecture Hall 2*

14:30 – 15:15 Keynote: **Anna Marciniak-Czochra**, University of Heidelberg (Germany) — *Lecture Hall 2*
Space-scale separation and pattern selection in mechano-chemical models of symmetry breaking

15:15 – 16:00 Keynote: **Ursula Klingmüller**, DKFZ (Germany) — *Lecture Hall 2*
Advancement of dynamic pathway modelling towards clinical translation

16:00 – 16:30 Coffee break — *Foyer*

16:30 – 18:00 Parallel sessions with invited and selected talks

	Modelling of Cellular Pathways 1 *Lecture Hall 7*	**Modelling of Endocrine Systems** *Lecture Halls 5+6*	**Mathematical Biology** 1 *Lecture Halls 3+4*
16:30 – 17:00	Invited talk: **Julio Banga**, MBG-CSIC (Spain) Climbing the Ladder of Inverse Problems in Computational Systems Biology	Invited talk: **Jae Kyoung Kim**, KAIST (Republic of Korea) From Blackboard to Bedside: Translating Mathematical Sleep Models into Samsung Galaxy Watch	Invited talk: **Marie Doumic-Jauffret**, Inria & École Polytechnique (France) Mathematical modelling to unravel the link between senescence and telomere length dynamics
17:00 – 18:00	Selected talks	Selected talks	Selected talks

18:00 Welcome Reception — *Foyer*

Tuesday, March 17, 2026

8:30 – 9:00 Welcome Coffee — *Foyer*

9:00 – 9:45 Keynote: **Bernd Bodenmiller**, University of Zurich & ETH Zurich (Switzerland) — *Lecture Hall 2*
Highly multiplexed imaging of tissues with subcellular resolution by imaging mass cytometry

9:45 – 10:30 Keynote: **Helen Byrne**, University of Oxford (UK) — *Lecture Hall 2*
Understanding the shape of vascular networks using topological data analysis

10:30 – 11:00 Coffee break — *Foyer*

11:00 – 12:30 Parallel sessions with invited and selected talks

	Bioinformatics and Biostatistics 1 *Lecture Hall 7*	**Tumor Microenvironment** 1 *Lecture Halls 5+6*	**Infectious Disease Modelling** 1 *Lecture Halls 3+4*
11:00 – 12:30	Selected talks	Invited talk: **Nils Blüthgen**, Charité & Humboldt-University Berlin (Germany) Modeling latent variables in pooled single cell screens unveils clinically relevant transcriptional modules induced by oncogenes	Selected talks
11:30 – 12:30		Selected talks	

12:30 – 13:45 Lunch — *University canteen (CAMPO)*

13:45 – 15:15 Parallel sessions with invited and selected talks

	Modelling of Cellular Pathways 2 *Lecture Hall 7*	**Mathematical Biology** 2 *Lecture Halls 5+6*	**Infectious Disease Modelling** 2 *Lecture Halls 3+4*
13:45 – 14:15	Invited talk: **Andreas Raue**, University of Augsburg (Germany) The Translational Gap in Mechanistic Modeling	Selected talks	Selected talks
14:15 – 14:45	Selected talks		
14:45 – 15:15		Invited talk: **Becca Asquith**, Imperial College London (UK) KIRs and T cell dynamics	

15:15 – 16:30 Poster session 1 (odd numbers) with coffee — *Foyer & seminar rooms 1-4*

16:30 Social events — *Arithmeum, „Haus der Geschichte“ or Bonn city center*

Wednesday, March 18, 2026

8:30 – 9:00	Welcome Coffee	*Foyer*
9:00 – 9:45	Keynote: **Christoph Zechner**, SISSA (Italy) Statistical inference of chromatin- and transcription dynamics in living cells	*Lecture Hall 2*
9:45 – 10:30	Keynote: **Dominic Grün**, University of Würzburg (Germany) Decoding the cellular circuitry of organ tissues	*Lecture Hall 2*
10:30 – 11:00	Coffee break	*Foyer*
11:00 – 12:30	Parallel sessions with invited and selected talks	

	Tumor Microenvironment 2 *Lecture Hall 7*	**Single-Cell Analysis** 1 *Lecture Halls 5+6*	**Mathematical Biology** 3 *Lecture Halls 3+4*
11:00 – 11:30	Selected talks	Invited talk: **Alexander Skupin**, LCBS (Luxembourg) Cell Fate Dynamics at Single-Cell Resolution Reveals Biological Mechanisms in Health and Disease	Invited talk: **Luciano Marcon**, CABD (Spain) The Network Basis of Pattern Formation: A Topological Atlas of Multifunctional Turing Networks
11:30 – 12:00		Selected talks	Invited talk: **Miri Adler,** The Hebrew University of Jerusalem (Israel) Introducing Hot and Cold Fibrosis: Insights from a Cell-Circuit Theory of Tissue Organization
12:00 – 12:30			Selected talks

12:30 – 13:45	Lunch	*University canteen (CAMPO)*
13:45 – 14:10	Invited talk: **Andreas Reichel**, Bayer AG (Germany) Mechanistic PK/PD Modelling of Targeted Protein Degradation: Transforming the Discovery of a Novel Therapeutic Modality	*Lecture Hall 2*
14:10 – 14:35	Invited talk: **Heinrich Huber**, Boehringer Ingelheim RCV (Austria) Translational Insights from Semi-Mechanistic Modelling of Tumour Growth	*Lecture Hall 2*
14:35 – 15:00	Invited talk: **Lorenzo Contento**, Pumas-AI Inc. A Deep Dive into Generative Scientific Machine Learning	*Lecture Hall 2*
15:00 – 15:45	Plenary discussion: Mathematical life sciences in the age of LLMs and AI bots	*Lecture Hall 2*
15:45 – 17:00	Poster session 2 (even numbers) with coffee	*Foyer & seminar rooms 1-4*
17:00 – 18:30	Parallel sessions with invited and selected talks	

	Modelling of Cellular Pathways 3 *Lecture Hall 7*	**Single-Cell Analysis** 2 *Lecture Halls 5+6*	**Mathematical Biology** 4 *Lecture Halls 3+4*
17:00 – 17:30	Invited talk: **Federico Bocci**, RIMLS (The Netherlands) Navigating the attractor landscape of single cells	Invited talk: **Pawel Paszek**, IPPT PAN (Poland) Memory, noise and infection: single-cell insights into innate immunity	Selected talks
17:30 – 18:30	Selected talks	Selected talks	

19:30	Conference dinner	*Restaurant RheinAue*

Thursday, March 19, 2026

8:30 – 9:00	Welcome Coffee	*Foyer*
9:00 – 9:45	Keynote: **Christina Leslie**, Memorial Sloan Kettering Cancer Center (USA) Decoding cell dynamics and spatial organization in immune responses and the tumor microenvironment	*Lecture Hall 2*
9:45 – 10:30	Keynote: **Jeroen van Zon**, AMOLF (The Netherlands) AI-driven single-cell tracking of homeostasis in organoids	*Lecture Hall 2*
10:30 – 11:00	Coffee break	*Foyer*
11:00 – 12:30	Parallel sessions with invited and selected talks	

	Bioinformatics and Biostatistics 2 *Lecture Hall 7*	**Organoids and Stem Cell Biology** *Lecture Halls 5+6*	**Mathematical Biology** 5 *Lecture Halls 3+4*
11:00 – 11:30	Selected talks	Selected talks	Invited talk: **Stephen Moore,** University of Cape Coast (Ghana) Retrospective Impact Quantification of Malaria Interventions in Ghana
11:30 – 12:30			Selected talks

12:30 – 13:00	Closing	*Lecture hall 2*

Selected Session Talks per Scientific Track

Bioinformatics and Biostatistics

Session 1 – Tuesday, March 17 | 11:00-12:30

- **Xin Lai**, Tampere University (Finland)
  HallmarkGraph: a cancer hallmark informed graph neural network for classifying hierarchical tumor subtypes
- **Alina Schenk**, University Hospital Bonn (Germany)
  A regularized Cox model for selecting interactions and time-varying covariate effects
- **Oliver Lemke, Charité** – Berlin (Germany)
  The role of metabolism in shaping enzyme structures over 400 million years of evolution
- **Franziska Kimmig**, University of Kiel & University Hospital Schleswig-Holstein (Germany)
  Molecular signatures of post-acute sequelae of COVID-19
- **Roy Gusinow**, University of Bonn (Germany)
  Federated Latent Transition Models for Post-Acute Infection Syndromes

Session 2 – Thursday, March 19 | 11:00-12:30

- **Laura Koebbe**, University Hospital Bonn (Germany)
  Rare functional variants in FBN2 are strong genetic determinants for bicuspid aortic valve disease
- **Cong Quan Ta**, University of Augsburg & DKFZ (Germany)
  Integration of proteomics data from cell lines and tumors to profile patient drug sensitivity
- **Lea Weber**, DKFZ (Germany)
  Reconstructing Stem-Cell Population Dynamics from Somatic-Mutation Phylogenies in Ageing Mice
- **Diego Valderrama**, SCAI (Germany)
  MultiNSDEs: Dose-Guided Neural SDEs for Simulating Real and Counterfactual Patient Trajectories
- **Lotta Eriksson**, Chalmers University of Technology & University of Gothenburg (Sweden)
  Sensitive detection of copy number alterations in low-quality liquid biopsy sequencing data
- **Manuel Huth**, University of Bonn (Germany)
  NoLimits.jl: A flexible Julia framework for nonlinear and latent-state mixed-effects modeling

Infectious Disease Modelling

Session 1 – Tuesday, March 17 | 11:00-12:30

- **Maylis Layan**, Institut Pasteur & Université de Paris (France)
  Impact of the COVID-19 pandemic on the acquisition of ESBL-producing Klebsiella pneumoniae in hospitals: a modelling study on the intensive care unit of Guadeloupe
- **Alan Rendall**, University of Mainz (Germany)
  Backward bifurcations and multistationarity
- **Julia Bicker**, DLR (Germany)
  A hybrid approach for the simulation of spatially-resolved susceptible-infected-recovered epidemics using the method of moments for stochastic reaction networks
- **Marvin Schulte**, Fraunhofer Institute for Industrial Mathematics ITWM (Germany)
  The influence of the mutation process on the long-term behavior of infectious diseases
- **Burcu Gürbüz**, University of Mainz (Germany)
  Modeling time-dependent vaccine efficacy and re-vaccination dynamics in an extended SIRS framework
- **Shrichand Bhuria**, EHESP Rennes (France)
  Modelling the Spread of Healthcare-Associated Infections through a Nationwide Patient-Based Network in France's Healthcare Settings

Session 2 – Tuesday, March 17 | 13:45-15:15

- **Nils Gubela**, Freie Universität Berlin (Germany)
  Modelling transient behaviour changes during the 2022 mpox outbreak using temporal adaptive networks
- **Alexandra Teslya**, Utrecht University (The Netherlands)
  From Classrooms to Communities: Modeling the Impact of School-Based Interventions for Future Pandemic Response

- **Fredrick Asenso Wireko**, KNUST (Ghana)
  Fractional-Order Modelling and Data-Driven Analysis of Lymphatic Filariasis Dynamics in Ghana
- **Sydney Paltra**, TU Berlin (Germany)
  Inferring Mobility Reductions from COVID-19 Disease Spread along the Urban-Rural Gradient
- **Henrik Zunker**, DLR (Germany)
  A semi-continuous Graph-ODE approach with flow-based formulations to avoid quadratic system growth in Lagrangian metapopulation models
- **Punya Alahakoon**, University of Oxford (UK)
  Enhancing epidemiological parameter inference using quantitative diagnostic data

Mathematical Biology

Session 1 – Monday, March 16 | 16:30-18:00

- **Carola Sophia Heinzel**, University of Freiburg (Germany)
  Statistical Test to compare the Linkage Model and the Admixture Model based on Central Limit Results
- **Saeed Salehi**, IIM-CSIC (Spain) & KU Leuven (Belgium)
  Understanding When Lotka–Volterra Models Fail in Microbial Community Analysis
- **Alexander Browning**, University of Melbourne (Australia)
  Heterogeneity in temporally fluctuating environments
- **Torkel Loman**, University of Oxford (UK)
  Parametric and Functional Identifiability for Universal Differential Equations

Session 2 – Tuesday, March 17 | 13:45-15:15

- **Hugo Dourado**, Heinrich Heine University (Germany)
  Growth Mechanics and the oscillatory biomass allocation in self-replicating cells
- **Lisa Li**, University Hospital Bonn (Germany)
  Towards data-based mathematical models of spatiotemporal immune-cell interactions
- **Gayathri Ramesan**, Max Planck Institute for Neurobiology of Behavior — Caesar (Germany)
  Critical dynamics generates slow manifolds for neural timing
- **Francis Tetteh Batsa**, AIMS (Ghana)
  A Fractional Derivative Approach to Model Anomalous Mass Transport in Atherosclerosis Plaque Formation

Session 3 – Wednesday, March 18 | 11:00-12:30

- **Harshavardhan BV**, Indian Institute of Science (India)
  Emergent dynamics of cellular decision making in multi-node mutually repressive regulatory networks
- **Inge Wortel**, Radboud University (The Netherlands)
  Cooperative motility emerges in crowds of T cells but not neutrophils

Session 4 – Wednesday, March 18 | 17:00-18:30

- **Jonas Braß**, Heinrich Heine University (Germany)
  Mechanistical modelling of C4 plants - hydraulics model
- **Kumaran Bala Kandan Viswanathan**, Radboud University (The Netherlands)
  Simulation-Driven Representation Learning for Cell Motility Data
- **Nils Becker**, DKFZ (Germany)
  Inference from Phylogenetic Somatic Variant Trees
- **Jan Rombouts**, Université Libre de Bruxelles (Belgium)
  Geometry, timescales and boundaries affect aggregation-based patterning in multicellular systems
- **Madhumita Mondal**, HBNI-IMSc (India)
  Node persistence from topological data analysis reveals changes in brain functional connectivity
- **Adrien Jolly**, Goethe University Frankfurt (Germany)
  Dynamical modeling-informed interpretation of Ki67 positivity

Session 5 – Thursday, March 19 | 11:00-12:30

- **Henrik Häggström**, Chalmers University of Technology & University of Gothenburg (Sweden)
  Simulation-based inference for stochastic nonlinear mixed-effects models with applications in systems biology

- **Mike van Santvoort**, Eindhoven University of Technology (The Netherlands)
  Modelling cell-cell interactions with random graphs
- **Gloria Agyeiwaa Botchway**, University of Ghana (Ghana)
  On a modified Leslie-Gower model with prey defense and predator cannibalism
- **Johannes Textor**, Radboud University (The Netherlands)
  What Does the Shape Space of T-Cell Epitopes Look Like?

Modelling of Cellular Pathways

Session 1 – Monday, March 16 | 16:30-18:00

- **Sophia Dehnen, University of Freiburg (Germany)**
  Condition-Specific Profile Likelihood Analysis: Visualizing how Individual Experimental Conditions Shape Parameter Estimates
- **Sebastian Persson**, The Francis Crick Institute (UK)
  PEtab SciML: The missing layer for scalable and flexible scientific machine learning modeling in biology
- **Nicole Radde**, University of Stuttgart (Germany)
  A population model reveals a surprising role of stochastic cell division in epigenetic memory systems
- **Yogesh Bali**, University of Mainz (Germany)
  Mechanochemical Energy Landscapes Under Force: Catch–Slip Bonds in T-Cell Activation

Session 2 – Tuesday, March 17 | 13:45-15:15

- **Jenny Geiger**, University of Stuttgart (Germany)
  Stochasticity contributes to explaining heterogeneity in mitochondrial engagement during apoptosis
- **Rifaldy Fajar**, IMCDS-BioMed Research Foundation (Indonesia)
  Mathematical Modeling of Canonical–Noncanonical NF-KB Crosstalk Driving Early CD8+ T-Cell Fate Bifurcation and Long-Term Effector–Memory Balance
- **Gesina Menz**, Uppsala University (Sweden)
  Multi-Framework Modelling of Population-Level Cellular Signalling
- **Mio Heinrich**, University of Freiburg (Germany)
  Flavours of Practical Identifiability: Sensitivities, Confidence, and Confusion

Session 3 – Wednesday, March 18 | 17:00-18:30

- **Paolo Odello**, NKI (The Netherlands)
  Dissecting the efficacy of Multiple Low Dose Efficacy via computational modelling of EGFR-MAPK inhibition
- **Jeanne Le Clézio**, CNRS & Université Côte d'Azur (France)
  Physical-Chemistry of Cell Physiology: a top-down, transdisciplinary approach from obvious biological statements to interwoven multiscale algebraic dynamical systems and the need for a tractable mathematical framework
- **Rune Höper**, University of Leipzig (Germany)
  A Manually-Curated Stoichiometric Core Model Of Liver Metabolism
- **Simon Beyer**, University of Freiburg (Germany)
  Quantitative Modeling Reveals Feedback Control of T Cell Receptor Trafficking and Surface Homeostasis

Modelling of Endocrine Systems

Monday, March 16 | 16:30-18:00

- **Belinda Lombard**, University of Birmingham (UK)
  Regulation of ultradian pulsatility and stress responses in the human HPA axis
- **Chloé Weckel,** Université de Tours & Université Paris-Saclay (France)
  Spatiotemporal modeling of signaling pathways: impact of endosomal compartmentalization and application to gonadotropin receptors
- **Rafael Arutjunjan**, University of Freiburg (Germany)
  Adapting Confidence Thresholds and Profile Likelihood Analysis to Small Sample Sizes

- **Celvic Coomber**, Zuse Institute & TU Berlin (Germany)
  Investigating endogenous opioids unravels the mechanisms behind opioid induced constipation, a mathematical modeling approach

Organoids and Stem Cell Biology

Thursday, March 19 | 11:00-12:30

- **Stefan Engblom**, Uppsala University (Sweden)
  From single cells to tumors: computational modeling and analysis of cell populations
- **Millicent Afrifa Opoku**, AIMS (Ghana)
  Geometry-dependent FGF4-ERK signalling drives epiblast-primitive endoderm proportioning in a Cellular Potts model of the human blastocyst
- **Lutz Brusch**, TU Dresden (Germany)
  Virtual Embryo: Blastocyst and Organoid Models in the Morpheus Simulation Framework
- **Xuan Zheng**, Hubrecht Institute (The Netherlands)
  Organoid cell fate dynamics in space and time
- **Ingmar Glauche**, TU Dresden (Germany)
  From data to dynamics: mechanistic models illuminate the clonal evolution of hematopoietic stem cells
- **Jasmitha Boovadira Poonacha**, University of Bonn (Germany)
  Influence of Culture Media Composition on Drug Sensitivity in CRC organoids

Single-Cell Analysis

Session 1 – Wednesday, March 18 | 11:00-12:30

- **Yang Zhao**, Karolinska Institutet (Sweden)
  Spatially resolving B cell clonal dynamics in human and murine tissues
- **Nadine van de Brug**, Vrije Universiteit Amsterdam (The Netherlands)
  Mapping cellular states over time using a hierarchical feature expectation maximization approach for Gaussian mixture modeling
- **Alexander Aivazidis**, EMBL (Germany)
  STORMI leverages CRISPR interventions, DNA sequence syntax and multi-lineage dynamics to infer the regulatory mechanisms governing cell state dynamics
- **Isabel Mensah**, KNUST (Ghana)
  WAVDeSc: A Wavelet Based Denoising Pipeline for single-cell RNA Sequencing Data Analysis

Session 2 – Wednesday, March 18 | 17:00-18:30

- **Stanislaus Stein**, BioQuant (Germany**)**
  Geometric Modeling of Developmental Velocities in Single-Cell Data
- **James Boyle**, University of Oxford (UK)
  Inferring Cell-Cell Dynamics from Cell Trajectory Data Using Deep Attention Networks, and the Mechanisms Underlying T Cell Behavioural Heterogeneity in the Response to Cancer
- **Clémence Fournié**, Université Paris Cité (France)
  Cell Trajectory Inference based on Schrödinger problem and a mechanistic model of stochastic gene expression
- **Tim Stohn**, Vrije Universiteit Amsterdam (The Netherlands)
  Detecting changes in protein-covariation in smooth cell-state changes

Tumor Microenvironment

Session 1 – Tuesday, March 17 | 11:00-12:30

- **Lara Schmalenstroer**, University of Duisburg-Essen (Germany)
  Mathematical Modeling of Persistent Treatment Responses After Targeted Radiotherapy in Cancer
- **Luke De Bretton-Gordon**, University of Oxford (UK)
  An Interdisciplinary Approach to Quantifying the Impact of T-Cell Exhaustion on the Tumour Microenvironment

- **Madhuri Majumder**, The Hebrew University of Jerusalem (Israel)
  Modulatory Principles of Cellular Interactions in Hierarchical Cell Organization
- **Lukas Kiwitz**, University Hospital Bonn (Germany)
  Quantitative analysis of CODEX multiplexed histological imaging data in the tumour microenvironment

Session 2 – Wednesday, March 18 | 11:00-12:30

- **Federica Eduati**, Eindhoven University of Technology (The Netherlands)
  Integrating spatial imaging and intracellular signaling to model emergent tumor–T cell dynamics with multiscale agent-based models
- **Paras Jain**, Indian Institute of Science (India)
  Modeling Epithelial-Mesenchymal Plasticity: A Driver of Immune Evasion in Cancer
- **Prihantini Prihantini**, IMCDS-BioMed Research Foundation (Indonesia)
  Mathematical Modeling of RNA Velocity Manifold Dynamics Identifies Immune–Metastatic State Transitions and Tertiary Lymphoid Structure Stability Landscapes in Hepatocellular Carcinoma
- **David Cicchetti**, Radboud University (The Netherlands)
  Creating Realistic and Controllable Synthetic Tumor Microenvironment Images Using Diffusion Models Conditioned on Simulation Images
- **Alirez Dostmohammadi**, University of Duisburg-Essen (Germany)
  Spatially Resolved Transcriptomics Reveals Microenvironment-Driven Heterogeneity in Cutaneous T-Cell Lymphoma

Poster Presentations per Scientific Track

Bioinformatics and Biostatistics

Poster Session 1 – Tuesday, March 17 | 15:15-16:30

Poster 9 **Reindorf Borkor**, Kwame Nkrumah University of Science and Technology (Ghana)
Improved Autism Spectrum Disorder Detection using Machine Learning Methods: An Integration of fMRI and RNA Seq Data

Poster 21 **Talip Yasir Demirtas**, University Hospital Bonn (Germany)
JANUS: Joint ANalysis for augmentation of clUSter specificity

Poster 29 **Jonas Guzik**, Bielefeld University (Germany)
Prediction of linear B cell epitopes using outlier detection and in-silico hydrolysis with protein language models

Poster 35 **Carolin Kaffiné**, University of Bonn (Germany)
Disentangling Familial and Syndromic Facial Features Using Latent Embedding Analysis

Poster 37 **Charles M. Kaumbutha**, German Center for Neurodegenerative Diseases (DZNE) (Germany)
Advancing Explainability in Machine Learning Models for Alzheimer's Disease Prediction

Poster 69 **Angela Shaw**, University Hospital Bonn (Germany)
The Inhibitome: A Genome-Wide Map of Inhibitory Gene Relationships

Poster 103 **Irene Yeboah**, Kwame Nkrumah University of Science and Technology (Ghana)
Intercellular Communication in Plasmodium-infected Liver Tissues: A Spatial Transcriptomics

Poster Session 2 – Wednesday, March 18 | 15:45-17:00

Poster 2 **Carolina Alvarez Garavito**, University of Bonn (Germany)
A Deep Learning Framework for Multi-Site Signal Peptide Cleavage Prediction

Poster 4 **Shubhi Ambast**,German Center for Neurodegenerative Diseases (DZNE) (Germany)
scGNNPred: Explainable graph neural networks for scRNA-seq-based phenotype classification

Poster 16 **Sina Dadmand**, German Cancer Research Center (DKFZ) (Germany)
Deciphering the effect of (R)-2-hydroxyglutarate (2-HG) on the tumor microenvironment of IDH mutant gliomas

Poster 24 **Mohammadamin Ghasemi**, University of Bonn (Germany)
Neural Stem Cells Reroute Metabolism Under SHH Stress in Parkinson's

Poster 52 **Simon Merkt**, University of Bonn (Germany)
Segmentation Strategies for Spatial Transcriptomics in Murine Adipose Tissue

Poster 56 **Luise Nagel**, Charité - Universitätsmedizin Berlin (Germany)
A covariation-based framework to model proteome network dynamics and phenotypic heterogeneity in Candida albicans

Poster 62 **Dilan Pathirana**, University of Bonn (Germany)
Groundwork for open-source nonlinear mixed-effects modeling and quantitative systems pharmacology, with SBML and Petab

Poster 64 **Clemens Peiter**, University of Bonn (Germany)
Modeling Vaccine-Induced Antibody Dynamics Using Nonlinear Mixed-Effects Models in Healthcare Workers

Poster 74 **Thomas Rohde**, University Hospital Bonn (Germany)
BaCoN (Balanced Correlation Network) improves prediction of gene buffering

Poster 86 **Lea Seep,** University of Bonn (Germany)
Decoding Kupffer Cell Programming in Maternal Obesity-induced Fatty Liver via Integrated Multi-Omics and Functional Analysis

Poster 90 **Shenwei Shi**, University Hospital Bonn (Germany)
Embedding-Based Annotation Method in Adipose Tissue Spatial Metabolomics

Poster 94 **Lisa Maria Steinheuer**, University Hospital Bonn (Germany)
Predicting Vedolizumab Response in IBD Patients Using a Multimodal Machine Learning Approach

Infectious Disease Modelling

Poster Session 1 – Tuesday, March 17 | 15:15-16:30

Poster 1 **Alfredo Acosta**, Friedrich-Loeffler-Institut, Institute of Epidemiology (IfE) (Germany)
Optimal Theory in Surveillance and Intervention Strategies for African Swine Fever and Highly Pathogenic Avian Influenza

Poster 7 **Karla Bonic-Babic**, University of Oxford (UK)
A comparison of three methods for estimating the probability of a major outbreak

Poster 11 **Aleksandr Bryzgalov**, Martin Luther University Halle Wittenberg (Germany)
Spectral radius–based analytical evaluation of how daily contact rate fluctuations influence infectious disease dynamics

Poster 15 **Sunhwa Choi**, National Institute for Mathematical Sciences (NIMS) (Republic of Korea)
Replacing Markovian Assumptions with Non-Markovian Reality in Epidemic Parameter Estimation

Poster 17 **Isabelle Cochrane**, University Hospital Bonn (Germany)
Use of a Scattered Light Integrating Collector (SLIC) for Point of Care Testing to detect bacteria in fluid samples from Prosthetic Joint Infections of the lower limb

Poster 19 **Monica Veronica Crankson**, University of Mines and Technology (Ghana)
Optimal control and cost-effectiveness analysis of a two-strain bacterial meningitis epidemic model: Insights for effective public health interventions

Poster 25 **Ransford Ganyo**, University of Cape Coast (Ghana)
Modelling the impact of autoimmune hepetatis on liver cirrhosis progression

Poster 27 **Carlotta Felicia Gerstein**, University of Bonn (Germany)
Modeling spatially heterogeneous infectious disease spread with chances and challenges

Poster 41 **Agbatan Fiacre Luc Kouderin**, Hausdorff Center for Mathematics (Germany)
A Cascade Framework for Quantifying the Operational Effectiveness of Insecticide-Treated Nets (ITNs) in Benin.

Poster 47 **Pascal Lukas**, FAU Erlangen-Nürnberg & Universitätsklinikum Erlangen (Germany)
Determining viral spread and innate immune dynamics in human respiratory epithelium

Poster 53 **Barbora Nemcová**, Karlsruhe Institute of Technology (Germany)
Unjustified Poisson assumptions lead to overconfident estimates of the effective reproductive number

Poster 55 **Nicholas Opoku**, African Institute for Mathematical Sciences (AIMS) Ghana (Ghana)
Understanding the Transmission and Spread of Drug Sensitive and Resistant Strains within a Population: A Mathematical Modelling Approach

Poster 63 **Sandra Rjeschni**, LMU University Hospital Munich (Germany)
Modeling vertical HIV transmission: a comparison with WHO high-risk assessment in the LIFE studies

Poster 67 **Nina Schmid**, University of Bonn (Germany)
Universal differential equations for wastewater-based epidemiology

Poster 71 **Oladimeji Samuel Sowole**, AIMS Research & Innovation Centre, Rwanda
Curvature-Weighted Transmission Improves Network Epidemic Prediction and Control

Poster 77 **Christoph Sticha-Kaiser**, Fraunhofer Institute for Translational Medicine and Pharmacology (Germany)
A General Deterministic Model of Ordinary Differential Equations for a Broad Variety of Different Diseases

Poster 79 **Alexandra Teslya**, University Medical Center Utrecht (The Netherlands)
Evaluating the impact and effectiveness of HIV testing strategies among men who have sex with men in the Netherlands

Poster 87 **Kilian Volmer**, University of Bonn (Germany)
Modelling a potential spread of Foot-and-Mouth disease on the German animal trading networks

Poster 89 **Karina Wallrafen-Sam**, University of Bonn (Germany)
Wastewater-Informed Agent-Based Modeling of Hepatitis E Transmission Dynamics

Poster 91 **Nils Waßmuth**, University of Bonn (Germany)
Comparison of Simulation-based Inference Methods for Stochastic Compartmental Models

Poster 95 **Anna Wendler**, German Aerospace Center (DLR) (Germany)
Models based on integro-differential equations for epidemic outbreaks

Poster 99 **Myrthe S. Willemsen**, University Medical Center Utrecht (The Netherlands)
A multi-country comparison of the impact of a potential HIV cure on HIV transmission dynamics

Poster 107 **Henrik Zunker**, German Aerospace Center (DLR) (Germany)
Graph Neural Network Surrogates to leverage Mechanistic Expert Knowledge towards Reliable and Immediate Pandemic Response

Mathematical Biology

Poster Session 1 – Tuesday, March 17 | 15:15-16:30

Poster 3 **Nissrin Alachkar**, University Hospital Bonn (Germany)
Dissecting CD8+ T cell dynamic responses in adoptive T-cell transfer therapy of melanoma

Poster 31 **Manuel Haas**, University of Bonn (Germany)
Learning Convex Temporal Regularizers for the Inverse Problem in ECGI

Poster 33 **Kushal Haldar**, University Hospital Bonn (Germany)
Dynamics of multi-team cell fate decision networks

Poster 51 **Robin Müller**, University Hospital Bonn (Germany)
Model Based Analysis Of The Mutational Landscape In Antibody Affinity Maturation

Poster 57 **Matthias Overmann**, Technical University Braunschweig (Germany)
Benchmarking precision matrix estimation methods for differential co-expression network analysis

Poster 81 **Jan Tietgen**, Kiel University (Germany)
Comparison of discrete modelling methods for biological neural networks

Poster 101 **Lin Wouters**, Radboud University (The Netherlands)
Fitting faster: speeding up parameter fitting in stochastic simulators through variance reduction

Poster Session 2 – Wednesday, March 18 | 15:45-17:00

Poster 6 **Jonas Arruda**, University of Bonn (Germany)
Simulation-Based Inference of Cell Migration Dynamics in Complex Spatial Environments

Poster 14 **Amatus Beyer**, University of Stuttgart (Germany)
Model-Based Design for Morphogen-Driven Spatial Patterns in Synthetic Biology

Poster 20 **Domagoj Doresic**, University of Bonn (Germany)
Efficient Integration of Binary Qualitative Data into ODE Model Estimation

Poster 34 **Paul Jonas Jost**, University of Bonn (Germany)
Making One Measurement Count: Efficient Dynamic Inference in Label-Based Models

Poster 36 **Moritz Kappes**, University of Bonn (Germany)
Finite Element Space-Time Total Generalized Variation Regularization with applications to transmembrane potentials in ECGI

Poster 40 **Rosa Kreider**, University Hospital Bonn (Germany)
A data-integrated framework for modeling cellular interactions with semi-Markov dynamics

Poster 46 **Carolin Lindow**, University of Heidelberg (Germany)
Transcriptome-structured population models for neural stem cells

Poster 54 **Josua Michael**, University of Freiburg (Germany)
Identifiability Analysis of Foundational Cardiac Electrophysiology Models: The Noble Model

Poster 60 **Antonio de Jesus Ortiz Gonzalez**, University of Bonn (Germany)
Bayesian Framework for Joint Motion-Compensated 3D MRI Reconstruction

Poster 70 **Lorena Pohl**, University of Bonn (Germany)
Mathematical modelling of electroporation

Poster 80 **Jan Dennis Schering**, Radboud University (The Netherlands)
Simulation-Based Inference of Realistic Intracellular Dynamics in Tissue-Scale CPMs through GPU Parallelization

Poster 82 **Joanna Schnorr**, University Hospital Bonn (Germany)
A mathematical framework for quantifying T cell expansion in acute and chronic regulatory contexts

Poster 92 **Priyotosh Sil**, The Institute of Mathematical Sciences (IMSc) (India)
Biologically meaningful regulatory logic enhances the convergence rate in Boolean networks and bushiness of their state transition graph

Poster 100 **Marc Vaisband**, University of Bonn (Germany)
Uncertainty-Aware Diversity Quantification via the Chinese Restaurant Process

Poster 102 **Szilard Varga**, FAU Erlangen-Nürnberg & Universitätsklinikum Erlangen (Germany)
Do metrics from ecology help to classify clonal immune dynamics from T cell receptor repertoire data?

Poster 108 **Thomas Zerjatke**, Technical University Dresden (Germany)
The digital bone marrow niche – A spatio-temporal in silico model of haematopoietic (stem) cells in their bone marrow microenvironment

Modelling of Cellular Pathways

Poster Session 1 – Tuesday, March 17 | 15:15-16:30

Poster 13 **Benjamin Castellaz**, University of Stuttgart (Germany)
Bridging Model and Data: A Parametrization-and-Projection Method for Overdetermined Stochastic Inverse Problems in Systems Biology

Poster 39 **Sahil Khan**, Max Planck Institute for Multidisciplinary Sciences (Germany)
APP-Driven Vaccine Design: A Quantitative Framework for Optimizing Epitope Presentation

Poster 45 **Torkel Loman**, University of Oxford (UK)
Catalyst: Fast and flexible modeling of reaction networks

Poster 75 **Jörn Starruß**, Technical University Dresden (Germany)
Morpheus 3.0: Spatial reaction dynamics in deforming cell shapes

Poster 83 **Francis Didier Tshianyi Mwana Kalala**, ULB & Université de Lubumbashi (Belgium / Congo)
STAT1–p53 Dynamics Program Cell Fate through p21 and PUMA

Poster 93 **Daniel Weindl**, University of Bonn (Germany)
PEtab, pyPESTO, and AMICI: A Reproducible and Efficient Pipeline for Simulation and Parameter Estimation of Dynamic Models

Poster Session 2 – Wednesday, March 18 | 15:45-17:00

Poster 8 **Rafael Arutjunjan**, University of Freiburg (Germany)
Robust Global Model Analysis via the Stochastic Profile Likelihood Approximation

Poster 10 **Severin Bang** University of Freiburg (Germany)
Beyond mechanistic modeling: bridging the gap from signaling to phenotypical readout

Poster 28 **Sina Glöckner**, Max Delbrück Center (Germany)
Multicellular modelling of canonical NF-kB signaling

Poster 30 **Stephan Grein**, University of Bonn (Germany)
Evaluating the Performance of Parallel Optimization Methods for Large-Scale Dynamic Models in Computational Systems Biology

Poster 32 **Julia Hafenbrak**, FAU Erlangen-Nürnberg & Universitätsklinikum Erlangen, Germany
Understanding CAR-T cell dynamics and therapeutic outcome for diffuse large B-cell lymphoma using mathematical modelling

Poster 44 **Nantia Leonidou & Clara Hennersdorf**, German Cancer Research Center (DKFZ) (Germany)
NephrESA: Machine learning-informed mechanistic mathematical modelling to optimize anaemia treatment

Poster 58 **Specioza Nambooze**, African Institute for Mathematical Sciences (AIMS) (Ghana)
Regulation of Notch signalling dynamics by cis-binding and cell neighborhood relationships.

Poster 76 **Patience Aba Sakyi**, African Institute for Mathematical Sciences (AIMS) (Ghana)
Modelling pattern formation in spatially discrete systems

Poster 88 **Paul Sellentin**, University of Freiburg (Germany)
Visual Insights into Complex Dynamical Systems via Flux Sensitivity Analysis

Poster 104 **Frederik Wieder**, Kiel University (Germany)
Elementary Flux Mode Sampling in Genome Scale Metabolic Networks

Poster 106 **Vincent Wieland**, University of Bonn (Germany)
Mathematical Modeling of the Aryl Hydrocarbon Receptor Pathway

Modelling of Endocrine Systems

Poster Session 2 – Wednesday, March 18 | 15:45-17:00

Poster 48 **Madhuri Majumder**, The Hebrew University of Jerusalem (Israel)
Design principles of interferon signaling in regulating cell-density-dependent behavior under Type 1 diabetes scenario

Poster 68 **Maren Philipps**, University of Bonn (Germany)
Modelling the HPA axis: Mechanisms and individual variability in a human cohort

Organoids and Stem Cell Biology

Poster Session 1 – Tuesday, March 17 | 15:15-16:30

Poster 5 **Nelli Blank-Stein**, University of Bonn (Germany)
Immune competence alters neurodevelopmental vulnerability to micro- and nanoplastic exposure in human brain organoids

Poster 61 **Sneha Pushpa Ramesan**, University of Bonn (Germany)
In silico and patient-derived organoid-based therapy recommendations for colon carcinomas

Poster 65 **Annika Rohde**, University of Bonn (Germany)
Glucose Uptake Assay to Study Functional Maturation of Intestinal Organoids

Poster Session 2 – Wednesday, March 18 | 15:45-17:00

Poster 42 **Michelle Krogemann**, University of Bonn (Germany)
Random Walks or Directed Paths? – Harvesting the Potential of 3D Modeling to Uncover the Impact of Ontogeny on Alveolar Macrophage Dynamics

Poster 50 **Perla Mallouk**, Université Paris Cité, MAP5 (France)
Mathematical Modeling of Neuroblastoma Growth Based on Tumoroid data

Poster 72 **Moritz Richter**, University of Bonn (Germany)
Prediction of Drug Response in Patient-derived Organoids using Large-Scale Mechanistic Models

Single-Cell Analysis

Poster Session 1 – Tuesday, March 17 | 15:15-16:30

Poster 43 **Sophia Krix**, b-it Bonn-Aachen International Center for Information Technology (Germany)
Integrative Single-Cell Modeling and TCR Repertoire Profiling Reveal a Sleep-Immune-Brain Axis in Early Alzheimer's Disease

Poster 49 **Karola Mai**, German Center for Neurodegenerative Diseases (DZNE) (Germany)
ConvexGating infers gating strategies from clusters in single cell cytometry data

Poster 73 **Jasper Spitzer**, University Hospital (Germany)
The AAtlas - Atlas of the Aorta in Health and Disease

Poster 97 **Lennart Wicker**, FAU Erlangen-Nürnberg & Universitätsklinikum Erlangen (Germany)
Mathematical Inference of T-cell Trafficking Dynamics from Single-Cell Snapshots

Poster Session 2 – Wednesday, March 18 | 15:45-17:00

Poster 66 **Katrin Perez Anderson**, University Hospital (Germany)
Mapping Lesion Niches: How Microglia Adapt to Recurrent Demyelination

Poster 78 **Ivan Savchuk**, German Center for Neurodegenerative Diseases (DZNE) (Germany)
Enhancing Clinical Immunology and Disease Diagnostics with Global Swarm Learning

Poster 96 **Madheshvaran Suresh**, University Hospital (Germany)
Understanding cross-regulation of type I IFN and TNF in innate immune cells using data-driven mathematical modelling

Poster 98 **Viviane Timmermann**, University of Freiburg (Germany)
Image-Based Quantification of Autophagosome Biogenesis

Tumor Microenvironment

Poster Session 1 – Tuesday, March 17 | 15:15-16:30

Poster 23 **Janne Frenz**, German Cancer Research Center (DKFZ) (Germany)
Simulation of ultra-high dose rate (UHDR) irradiations using a Monte Carlo-based dose engine

Poster 59 **Jörg Peter**, German Cancer Research Center (DKFZ) (Germany)
Incorporating tumor growth models into physical simulation of radiological, nuclear medicine, and optical imaging systems

Poster 85 **Gemma van der Voort**, University of Bonn (Germany)
Enhanced neutrophil infiltration and distinct spatial patterning in non-draining lymph nodes under adoptive T cell therapy in murine melanoma

Poster 105 **Yixuan Zeng**, University Hospital (Germany)
Helminth-Induced Immune Training and Its Potential Impact on Tumor Progression

Poster Session 2 – Wednesday, March 18 | 15:45-17:00

Poster 12 **Florian Bartsch**, Max Delbrück Center & Charité - Universitätsmedizin Berlin (Germany)
Graph-Based Modeling of Spatial Organization in Developing and Tumor Tissues

Poster 18 **Luke De Bretton-Gordon**, University of Oxford (UK)
Learning Density-Dependent Cell-Cycle Regulation with UDEs

Poster 22 **Suman Gare**, University Hospital (Germany)
Data-driven multi-scale modeling of the tumor micro-environment using interpretable machine learning

Poster 26 **Nakshatra Ghosh**, University Hospital (Germany)
Mathematical Modeling of EMT Pathways in Cancer Invasion Through PDEs

Poster 38 **Tugberk Kaya**, University Hospital (Germany)
Tissue Microarray-Based Spatial Transcriptomics Defines TME in Cholangiocarcinoma

Poster 84 **Koert Schreurs**, Radboud University (The Netherlands)
Predicting T cell motility from a single image

All contributors by category and in alphabetical order with page number of/link to abstract

All contributors by category and in alphabetical order with page number of/link to abstract

Selected Talk Speakers in alphabetical order 47

All contributors by category and in alphabetical order with page number of/link to abstract

All contributors by category and in alphabetical order with page number of/link to abstract

All contributors by category and in alphabetical order with page number of/link to abstract

All contributors by category and in alphabetical order with page number of/link to abstract

All contributors by category and in alphabetical order with page number of/link to abstract

Abstracts

Bernd Bodenmiller

Department of Quantitative Biomedicine, University of Zurich, Switzerland; Institute for Molecular Health Sciences, ETH Zurich, Switzerland

Highly multiplexed imaging of tissues with subcellular resolution by imaging mass cytometry

Cancer is a tissue disease where heterogeneous tumor cells, stromal cells and immune cells form a dynamic ecosystem that evolves to support tumor expansion and ultimately tumor spread. The complexity of this system is the main obstacle to treat cancer. The study of the tumor ecosystem and its cell-to-cell communications is thus essential to enable an understanding of tumor biology, to define new biomarkers, and to identify new therapeutic routs and targets.

To understand the workings of the tumor ecosystem, highly multiplexed image information of tumor tissues is essential. Such multiplexed images will reveal which cell types are present in a tumor, their functional states, and how they interact together. To enable multiplexed tissue imaging, we developed imaging mass cytometry (IMC), a novel imaging modality that uses metal isotopes as reporters and currently allows to visualize over 50 antibodies and DNA probes simultaneously with subcellular resolution. In the near future, we expect that over 100 markers can be visualized. We applied IMC for the analysis of breast cancer samples in a quantitative manner. To extract biological meaningful data and potential biomarkers from this dataset, we developed a novel computational pipeline called histoCAT geared for the interactive and automated analysis of large scale, highly multiplexed tissue image datasets. Our analysis reveals a surprising level of inter and intra-tumor heterogeneity and identify new diversity within known human breast cancer subtypes as well as a variety of stromal cell types that interact with them.

In summary, our results show that IMC provides targeted, high-dimensional analysis of cell types, cell states and cell-to-cell interactions within the tumor ecosystem. Spatial relationships of complex cell states of cellular assemblies can be inferred and potentially used as biomarkers. We envision that IMC will enable a systems biology approach to understand and diagnose disease and to guide treatment.

Helen Byrne

Mathematical Institute, University of Oxford, UK

Understanding the shape of vascular networks using topological data analysis

High-resolution imaging technologies now enable quantitative reconstruction of vascular networks in two and three dimensions, offering unprecedented opportunities to study how vascular architecture changes during development, disease progression, and treatment response. These datasets are rich and biologically informative, but their geometric and topological complexity makes systematic quantification non-trivial and exposes the limitations of traditional descriptors such as vessel density, branching statistics, or graph-theoretic measures.

In this talk, I will introduce topological data analysis (TDA), a mathematical framework that characterises the structure—or “shape”—of complex datasets. I will show how TDA provides concise descriptors of vascular networks that complement more traditional geometric or graph-based metrics, and illustrate how they can be adapted to the specific challenges posed by vascular imaging data. Through a series of case studies, I will show how TDA can be used to detect and quantify treatment-induced vascular remodelling, compare vascular networks across experimental conditions, and integrate vascular topology with **computational models of vascular growth** via parameter inference and model selection. Together, these examples illustrate how methods from TDA can be used to increase our understanding of how vascular structure and remodelling influence physiological and pathological processes and also to link mechanistic models with high-dimensional imaging data.

Dominic Grün

Institute of Systems Immunology, University of Würzburg, Germany

Decoding the cellular circuitry of organ tissues

Mathematical modeling of gene networks in systems biology has uncovered key design principles underlying network motifs that regulate transcriptional responses. Comparable engineering principles are thought to control the interactions of molecular response programs among neighboring cells within local tissue environments. These cellular circuits play a critical role in governing tissue development, maintaining homeostasis, and mediating responses to disease. Recent advances in spatial transcriptomics now enable precise measurement of cellular states within tissues; however, existing computational methods are largely descriptive and lack the capacity to predict these circuits or their downstream effects on cellular behavior. We introduce latent variable modeling approaches to integrate single-cell RNA-sequencing and high-resolution imaging-based spatial transcriptomics data for the inference of cellular circuitry. Focusing on bone marrow regeneration after CAR-T cell therapy of multiple myeloma patients, this modeling paradigm reveals a cellular niche network of immune cells and stromal cells, that sustains an inflamed bone marrow microenvironment and impedes the reestablishment of healthy hematopoiesis, leading to prolonged cytopenia – a severe side effect of CAR-T cell therapy.

Ursula Klingmüller

Systems Biology of Signal Transduction, German Cancer Research Center (DKFZ), Heidelberg, Germany

Advancement of dynamic pathway modelling towards clinical translation

Diseases are dynamic processes that are caused by the deregulation of intracellular information processing through complex signal transduction networks. To resolve key regulatory mechanism dynamic pathway models have been instrumental. However, the availability of time-resolved data on multiple systems components has been limiting. Therefore, we developed SmartPhos, a multistep experimental and computational pipeline, optimized for low-input and high-throughput applications in mass spectrometry-based proteomics. We show that this pipeline now allows us to reconstruct the protein phosphorylation dynamics in entire signal transduction pathways. To evaluate the potential of mechanistic modelling in resolving disease related mechanisms, we assessed the impact of non-opioid analgesic pain killers on IL-6-induced acute-phase responses in liver cells. Using proteomics and dynamic pathway modeling, we show that diclofenac (DCF) and paracetamol (APAP) directly impact IL-6 induced response. While in non-cancerous hepatocytes the strength of the IL-6-induced negative feedback loop determines the patient-specific impact of the pain killers on the expression of the key regulator of iron metabolism, hepcidin, in hepatoma cells both pain killers amplify the IL-6 induced expression of hepcidin by an autocrine BMP secretion loop, potentially fostering anemia. Anemia is a condition characterized by a reduced number of red blood cells (erythrocytes), which contain the oxygen-carrying protein hemoglobin (Hb). The key regulator of the production of erythrocytes is the hormone erythropoietin (Epo), which is produced by the kidney. Due to the impaired functionality of the kidney, patients with chronic kidney disease (CKD) suffer from anemia. We advance a multiscale dynamic pathway model for anemia treatment in CKD patients by erythropoiesis-stimulating agents (ESAs) and demonstrate the potential of our approach to optimize the treatment for individual patients.

Christina Leslie

Computational & Systems Biology. Memorial Sloan Kettering Cancer Center, NY, USA

Decoding cell dynamics and spatial organization in immune responses and the tumor microenvironment

We will present new ML/AI models for single-cell multiome (scRNA+ATAC-seq) and imaging-based spatial transcriptomics with applications to decoding immune cell state dynamics and the organization of the tumor microenvironment. First, we will present a generative neural ordinary differential equation (ODE) model for single-cell multiome data called DynaVelo, which we use to learn a functional form of the dynamics — corresponding to learned RNA velocity and transcription factor (TF) motif velocity vector fields — of wildtype and mutant germinal center B cells. We show that Jacobian analysis or in silico perturbations can recover dynamic regulatory networks governing cell state transitions in the germinal center. We also show how to predict the impact of genetic loss-of-function mutations on cell dynamics, and how to predict TF perturbations that rescue loss-of-function phenotypes. Second, we will present a new discrete representation learning model for annotating neighborhoods and cells in imaging-based spatial transcriptomics (ST) by exploiting pixel-level transcript information, without using cell segmentation or converting ST data to a cell-by-gene matrix. We apply our model to ST data profiling pancreatic ductal adenocarcinoma (PDAC) tumors from Memorial Sloan Kettering patients to decode the local microenvironment of perineurally invaded versus non-invaded nerves.

Anna Marciniak-Czochra

Institute for Mathematics, Heidelberg University, Germany

Space-scale separation and pattern selection in mechano-chemical models of symmetry breaking

In this talk, I will present a new mechanochemical, PDE-based framework validated by recent experiments on regenerating epithelia, with Hydra as a model system. The model couples morphogen reaction–diffusion dynamics with tissue mechanics via a positive feedback loop: mechanical strain enhances morphogen production, while morphogen concentration modulates tissue elasticity. Global strain conservation induces a nonlocal inhibitory effect, yielding a mechanochemical realisation of the local activation–long-range inhibition principle. For an exponential elasticity–morphogen coupling, the system admits a variational structure that enables a rigorous analysis of steady states. Stability analysis explains the selective emergence of single-peaked patterns, while multimodal states are unstable. Bifurcation analysis uncovers both supercritical and subcritical pitchfork bifurcations, as well as fold bifurcations giving rise to bistability Together, these results show that mechanochemical feedback alone is sufficient to robustly generate single-peaked patterns in regenerating tissues—without invoking a second diffusible inhibitor. The analytical findings are complemented by experimental validation of the model.

Jeroen van Zon

Department of Autonomous Matter, AMOLF, Amsterdam, The Netherlands

AI-driven single-cell tracking of homeostasis in organoids

During development and homeostasis, intricate patterns and structures arise and are maintained on the level of tissues and organs, yet ultimately this results from the dynamics of individual cells, as given by their divisions, movements and gene expression. However, linking the behavior of cells across time- and length-scales to the emergence of large-scale tissue structures remains challenging. Here, I will discuss how we use quantitative single-cell tracking to understand how the intestinal epithelium organizes itself into a highly robust spatial pattern of stem and differentiated cells. First, I will present an AI-driven workflow we developed that allows automated tracking of all cells in intestinal organoids. Next, I will show how such a cell-tracking approach revealed that WNT signaling controls intestinal stem cell maintenance and cell differentiation not through a spatial gradient model, as is commonly thought, but instead via a timer mechanism.

Christoph Zechner

Scuola Internazionale Superiore di Studi Avanzati (SISSA), Trieste, Italy

Statistical inference of chromatin- and transcription dynamics in living cells

Recent live-cell microscopy techniques allow the simultaneous tracking of distal genomic elements and transcriptional activity, offering new ways to study chromatin dynamics and gene regulation. However, drawing robust conclusions from such data is statistically challenging due to substantial technical noise, intrinsic fluctuations and limited time resolution. In this talk I will discuss recent progress we have made in addressing these challenges. First, I will present a statistical method to quantify CTCF/cohesin-mediated chromatin looping dynamics from two-point live-cell imaging experiments. The method combines a simple polymer model with Bayesian filtering to infer loop lifetimes and frequencies. Its application to experimental measurements of the *Fbn2* loop in mouse embryonic stem cells revealed that chromatin loops are surprisingly rare and short-lived. I will then discuss how simultaneous transcriptional readouts (MS2/PP7) could be integrated with chromatin tracking data to quantify enhancer-promoter communication and its effect on transcription. I will conclude by highlighting potential implications of such approaches for understanding gene regulation in single cells and outline current and future challenges

Miri Adler

The Alexander Silberman Institute of Life Sciences, The Hebrew University of Jerusalem, Israel

Introducing Hot and Cold Fibrosis: Insights from a Cell-Circuit Theory of Tissue Organization

Fibrosis is pathological scarring following tissue injury and a major cause of morbidity and mortality worldwide. Because fibrotic remodeling involves thousands of interacting factors, progress in mechanistic understanding and therapy requires principled simplification. In this talk, I will introduce a cell-circuit theory we recently developed for interactions between myofibroblasts and macrophages - the two cell types that produce and remodel the scar. The theory predicts two distinct pathological regimes: hot fibrosis, characterized by coupled expansion of macrophages and myofibroblasts, and cold fibrosis, dominated by myofibroblasts with limited macrophage involvement. I will show how we combine this theoretical framework with computational analyses to identify therapeutic targets for reducing fibrosis, including regulators of myofibroblast proliferation. Finally, I will discuss experimental validation of these predictions in the heart across two clinically relevant injury settings, myocardial infarction and heart failure, which lead to distinct fibrotic states consistent with the hot and cold regimes predicted by the theory. Together, this circuit-to-target approach links tissue-organization principles to testable predictions and therapeutic strategies for fibrotic disease across diverse organs.

Becca Asquith

Department of Infectious Disease, Imperial College London, UK

KIRs and T cell dynamics

Studying immunology in humans is extremely challenging, for obvious ethical reasons. Mathematics, combined with experiment, can provide a unique and valuable insight. We will focus on a family of immune receptors called KIRs (killer immunoglobulin like receptors). We combine analysis of genetic data from large patient cohorts with mechanistic mathematical modelling and assays of in vitro and in vivo T cell dynamics to gain insight into the relationship between iKIRs, T cell dynamics and human health. We suggest that KIRs enhance T cell survival and that this in turn impacts on clinical outcome in viral infection (HCV, HTLV-1, HIV-1) and autoimmunity (type I diabetes).

Julio R. Banga

Computational Biology Lab, MBG-CSIC, Pontevedra, Spain

Climbing the Ladder of Inverse Problems in Computational Systems Biology

The inherent complexity of cellular pathways, characterized by high-dimensional, nonlinear, and multiscale dynamics, presents formidable challenges for predictive modeling. A cornerstone of computational systems biology is the ability to reconstruct these pathway models from sparse, noisy, and incomplete experimental data. This talk introduces a hierarchical framework for addressing the inverse problem in biological modeling, spanning the spectrum from traditional parametric estimation to the characterization of hidden optimality principles and multi-agent strategic interactions.

We begin with an analysis of the standard model calibration problem for state-space ordinary differential equations, highlighting the roles of structural and practical identifiability. Moving beyond fixed architectures, we then examine the automated discovery of model topologies, with a specific focus on the challenges of structural distinguishability. Next, we explore more generalized formulations of the inverse problem: the inference of underlying optimality principles through bilevel inverse optimal control and the modeling of competitive biological behaviors via inverse differential games. While these advanced formulations hold significant potential for deepening our mechanistic understanding, they are particularly demanding due to their inherent ill-posedness and non-convexity. We conclude by discussing these challenges and proposing potential strategies for their mitigation.

References

- Banga JR, Sager S. Generalized Inverse Optimal Control and its Application in Biology. *Annu. Rev. Control*. 2025;60:101029. doi:10.1016/j.arcontrol.2025.101029
- Tsiantis N, Balsa-Canto E, Banga JR. Optimality and identification of dynamic models in systems biology: an inverse optimal control framework. *Bioinformatics*. 2018;34(21):3780. doi:10.1093/bioinformatics/bty438

Nils Blüthgen

Institute for Theoretical Biology, Charité – Universitätsmedizin Berlin & Humboldt-Universität zu Berlin, Germany

Modeling latent variables in pooled single cell screens unveils clinically relevant transcriptional modules induced by oncogenes

Oncogenic mutations shape colorectal cancer (CRC) biology, yet their impact on transcriptional phenotypes remains incompletely understood, and their individual prognostic value is limited. Here, we perform a pooled single-cell transcriptomic screen of over 100,000 CRC cells with a comprehensive barcoded library of oncogenic variants across genetically diverse CRC lines. Using a variational autoencoder-based interpretable factor model, we identify ten conserved oncogene-driven transcriptional modules (TMOs) representing core cancer phenotypes such as cellular plasticity, inflammatory response, replicative stress, and epithelial-to-mesenchymal transition. Engagement of these modules can be context-dependent, reflecting interactions between oncogene-induced driver pathways and background genetics. TMO activity in patient tumors stratifies CRC cohorts into high- and low-risk groups, improving relapse-free survival prediction beyond existing classification systems. Our study systematically links oncogenic signaling to transcriptional states and clinical outcomes, establishing a functional framework for module-based patient stratification in precision oncology.

Federico Bocci

Radboud Institute for Molecular Life Sciences (RIMLS), Radboud University, Nijmegen, The Netherlands

Navigating the attractor landscape of single cells

Modern single cell sequencing technologies enable us to probe cellular processes at unprecedented resolution, while introducing new theoretical challenges. A major difficulty lies in constructing dynamical models of cell behavior, as these technologies capture only a single snapshot of a cell's state, thereby preventing the observation of temporal dynamics. In this talk, I will discuss how we utilized single cell transcriptomics—a technique that measures RNA expression in individual cells—to develop a mathematical framework of gene expression and construct the attractor landscape regulating cell fate decisions. By applying this model under both equilibrium and non-equilibrium conditions, we analyzed the stability, transition paths, and cell type-specific regulatory networks that govern cell fate. Building on this framework, we introduce a single cell transition tensor that harmonizes small stochastic fluctuations in gene expression at a local level (within individual attractors) with global changes in cell fate (transitions between attractors) to dissect cellular dynamics across multiple scales. Finally, we incorporate spatial transcriptomics data into our framework to project cell fate transitions in space.

Key publications:

- Bocci F, Zhou P, Nie Q. spliceJAC: transition genes and state-specific gene regulation from single-cell transcriptome data. *Mol Syst Biol.* 2022;18(11):e11176. doi:10.15252/msb.202211176
- Barcenas M, Bocci F, Nie Q. Tipping points in epithelial-mesenchymal lineages from single-cell transcriptomics data. *Biophys J.* 2024;123(17):2849-2859. doi:10.1016/j.bpj.2024.03.021
- Zhou P, Bocci F, Li T, Nie Q. Spatial transition tensor of single cells. *Nat Methods*. 2024;21(6):1053-1062. doi:10.1038/s41592-024-02266-x

Lorenzo Contento

Pumas-AI Inc.

A Deep Dive into Generative Scientific Machine Learning

Mechanistic modelling leverages scientific insight into a phenomenon to produce interpretable models that generalize well even when fitted on small datasets, while machine learning (ML) is a completely data-driven approach that does not require any prior knowledge but results in blackbox models that are prone to overfitting. Scientific Machine Learning (SciML) tries to combine the strengths of the two approaches by allowing mechanistic understanding to limit the model expressivity (excluding unreasonable model structures and enhancing generalization ability) while still allowing data-driven flexibility where prior knowledge is lacking.

In many applications such as pharmacometrics we are not content with modelling a process for a single subject but we want to describe a heterogeneous population of subjects. This is usually achieved using a non-linear mixed-effects (NLME) model in which some parameters are shared across subjects (population parameters) and others are subject-specific (individual parameters). In practice, an NLME model describes the distribution of the response of interest in the population and is thus an example of a generative model. By combining mechanistic and data-driven components, we can build very powerful Generative SciML (GenSciML) models that can be trained on relatively small populations and yet be able to generalize well.

Generative ML models such as variational auto-encoders (VAEs) can perform dimensionality reduction by encoding complex data with a few latent variables. NLME models do the same by encoding the response of a subject (e.g., a timeseries of drug responses) using a few individual parameters. Such a parallel allows us to extend the wealth of results and insights from the field of generative ML to NLME models. In particular, it suggests that NLME models for timeseries can be linked to existing generative models for other data modalities through their latent spaces.

Marie Doumic-Jauffret

Center for Applied Mathematic, Merge project-team, Inria & École Polytechnique, France

Mathematical modelling to unravel the link between senescence and telomere length dynamics

Progressive shortening of telomeres ultimately causes replicative senescence and is linked with aging and tumor suppression. In this talk, we develop mathematical models - both with stochastic branching processes and their deterministic limits - for telomere shortening and re-elongation, analyse them and compare them quantitatively to data from Saccharomyces cerevisiae. This reveals selection forces within a population and the sources for heterogeneity in individual cell fates. Our results offer a comprehensive framework for investigating the implications of telomere length on human diseases.

Heinrich Huber

Boehringer Ingelheim RCV GmbH & Co KG, Division Drug Discovery Sciences, Vienna, Austria

Translational Insights from Semi-Mechanistic Modelling of Tumour Growth

Oncology drug discovery begins with a rigorous preclinical filtering process that spans in vitro studies, in vivo evaluation in preclinical species, and the projection of pharmacokinetics (PK) and pharmacodynamics (PD) from animals (mouse, rat, dog) to human patients. Early in this workflow, large numbers of candidate molecules are screened for potency, selectivity, and developability. In vitro cellular assays first identify compounds with promising potency (IC_{50} values), after which only a small subset advances into in vivo xenograft models. At this stage, in vitro–to–in vivo correlations (IVIVC) become critical. Compounds must achieve sufficient free drug exposure in vivo to cover their in vitro IC_{50} and elicit measurable tumor growth inhibition. PK/PD modeling plays a central role in this evaluation: by linking in vitro IC_{50} values to in vivo blood exposure and tumor growth dynamics, these models help predict which compounds can achieve stasis doses and which are unlikely to reach meaningful therapeutic coverage.

In this talk, I present a semi-mechanistic framework that describes how compound exposure, IC_{50} coverage, and tumor-specific growth characteristics—along with tumor permeability to the compound—govern efficacy. This modeling approach explains much of the variability observed in classical IVIVC analyses and clarifies when PK profile features, such as peak-to-trough ratios, meaningfully influence response. Finally, I outline how this framework can be extended to support clinical dose selection.

Jae Kyoung Kim

Korea Advanced Institute of Science and Technology (KAIST), Daejeon, Republic of Korea

From Blackboard to Bedside: Translating Mathematical Sleep Models into Samsung Galaxy Watch

Mathematical models of sleep regulation describe how homeostatic sleep pressure and the circadian pacemaker interact to generate stable sleep–wake cycles. These dynamics are tightly coupled to endocrine rhythms, including daily oscillations of Cortisol and Melatonin, which influence alertness, metabolism, and mood stability. Yet translating these mechanistic insights into real-world applications remains challenging. In this talk, I present how physiologically grounded sleep models were integrated with wearable sensor data to infer latent biological states—such as sleep pressure and circadian phase—from noisy, free-living environments. Embedding dynamical structure into machine learning improves interpretability while preserving endocrine relevance. This framework was translated into personalized Bedtime Guidance implemented in the Samsung Galaxy Watch, enabling large-scale circadian alignment in daily life. We show that stable phase timing and adequate sleep pressure dissipation are associated with enhanced next-day alertness, improved sleep quality, and reduced markers of mood instability. This work demonstrates how mathematical theory can extend beyond the blackboard to become a scalable platform for digital endocrine health and precision chronomedicine.

Luciano Marcon

Andalusian Center for Developmental Biology, Sevilla, Spain

The Network Basis of Pattern Formation: A Topological Atlas of Multifunctional Turing Networks

Understanding how genetic networks can drive different self-organizing spatial behaviors remains a significant challenge. Here, we use an automated algebraic method to systematically screen for Turing networks capable of generating diverse spatial patterns from noise, including periodic static waves, traveling waves and noise-amplifying patterns. We organize these networks into a higher-level graph (topological atlas) where nodes represent Turing networks linked together when they differ by only one regulatory interaction. In this atlas, Turing networks are arranged into distinct clusters showing a remarkable correspondence between network topology and self-organizing behaviors. Using an analytical approach, we identify the specific regulatory feedbacks that characterize each behavior. Moreover, we discover that different clusters are interconnected by multifunctional networks that can transition between behaviors upon feedback modulation. Among these networks, we find a new class of multiphase Turing networks capable of altering the phase of periodic wave patterns depending on the parameters, and networks that can transition between static and oscillatory Turing behaviors. The atlas further highlights the crucial role of feedback on immobile nodes in regulating pattern formation speed and precision by canalizing system noise. Overall, our study provides a novel framework to study the evolution and development of multicellular self-organization through changes in network topology and feedback modulation. This offers insights into how genetic regulatory networks can be tuned to drive pattern formation in developmental biology and in stem cell systems like embryoids and organoids.

Stephen Moore

University of Cape Coast, Cape Coast, Ghana

Retrospective Impact Quantification of Malaria Interventions in Ghana

Malaria remains a major public health issue in sub-Saharan Africa, particularly in the Northern Region of Ghana. This study focuses on Karaga, Gushegu, and Tatale districts, using both ordinary differential equation (ODE) and stochastic differential equation (SDE) models to assess the impact of Indoor Residual Spraying (IRS). The SDE model includes Brownian motion to capture the effects of randomness, comparing malaria progression with and without stochastic perturbations. Seasonality is modeled using a Fourier series with second harmonics, fitted to precipitation data via non-linear least squares. The effectiveness of IRS is represented using an exponential decay function modeling vector mortality over 6- and 12-month periods. Key parameters, including the mosquito biting rate (α) and transmission rate λ_v, were calibrated to fit observed prevalence data, allowing for comparisons between observed and estimated prevalence. Disease-free equilibrium and the basic reproduction number ($\mathcal{R}_0^{\mathcal{D}}$) were derived for both deterministic and stochastic models, and stability analyses were performed. Sensitivity analysis using One-At-a-Time (OAT) with partial derivatives was conducted to identify key parameter influences on malaria transmission. The Milstein method was employed for stochastic simulations, while the Euler method was used for deterministic ones. IRS intervention outcomes were validated using least square error against pre-intervention data over a 96-month period. Results show IRS reduces transmission, though its efficacy depends on timing, coverage, and the influence of asymptomatic carriers. This analysis provides insights into optimizing IRS-based malaria control strategies in endemic regions like Northern Ghana.

Pawel Paszek

Department of Biosystems and Soft Matter, Institute of the Fundamental Technological Research Polish Academy of Sciences, Warsaw, Poland

Memory, noise and infection: single-cell insights into innate immunity

Activation of immune responses is inherently heterogenous, resulting in diverse outcomes of the host-pathogen interactions at the single cell level. To understand the regulation of antibacterial innate immune responses, we combine mathematical modelling with single-cell approaches including quantitative microscopy and genomics to dissect variability within the Toll-like receptor system and during bacterial infection. We show that inducible genes follow distinct stochastic regulatory architectures, yet their variability is constrained trough modulation of transcriptional bursting. Extending this analysis across clonal populations, we identified subset of TLR genes that exhibit transcriptional memory over many cell divisions. This heritability interacts with population context to generate distinct regulatory regimes, ranging from stable clonal divergence to transient, environmentally constrained inflammatory responses. Importantly, heritable gene expression determines clonal susceptibility to *Listeria monocytogenes* infection, directly linking transcriptional memory to heterogenous infection outcomes. Together these findings reveal how transcriptional noise and memory shape innate immunity and infection outcomes.

Andreas Raue

University of Augsburg, Germany

The Translational Gap in Mechanistic Modeling

Mechanistic modeling of cellular signaling pathways has generated important biological insights, yet its impact on clinical decision-making remains limited. A key challenge lies in bridging the gap between well-controlled experimental systems and the complexity and heterogeneity of patient populations, as well as linking short-term molecular signaling events to long-term clinical outcomes.

This presentation discusses strategies to address this translational gap by combining mechanistic pathway models with data-driven approaches, including hybrid modeling frameworks and single-cell data integration. Examples from oncology illustrate how such approaches can support hypothesis generation, improve prediction of treatment response, and guide the development of novel therapeutic strategies.

Andreas Reichel

Bayer AG, R&D - Preclinical Development, Berlin, Germany

Mechanistic PK/PD Modelling of Targeted Protein Degradation: Transforming the Discovery of a Novel Therapeutic Modality

Target degradation is a novel therapeutic modality that aims at removing rather than inhibiting disease-related proteins. Due to the simultaneous kinetics of the drug and the target protein, mechanistic modelling is required to understand, optimize and predict the behaviour of targeted protein degraders (TPDs).

The talk illustrates how mechanistic PK/PD modelling can rationally guide TPD discovery through quantitative prediction of *in vivo* degradation profiles from *in vitro* degradation data, delineating key compound properties, impacting experimental study design, and translating *in vitro* data to the *in vivo* situation.

Case examples will be shown i) applying PK/PD modeling for compound selection and progression, ii) estimating of target occupancy, iii) generating a translational strategy tailored for TPDs, and iv) investigating both expected and unexpected changes related to the unique mode-of-action of targeted protein degraders after repeated dosing.

Alexander Skupin

Luxembourg Centre for Systems Biomedicine (LCBS), Integrative Cell Signalling, University of Luxembourg, Luxembourg

Cell Fate Dynamics at Single-Cell Resolution Reveals Biological Mechanisms in Health and Disease

Cell fate is a dynamic, stochastic process governed by high-dimensional gene regulatory networks whose stable cell identities correspond to attractor states in a complex transcriptional landscape. While single-cell technologies have transformed our ability to resolve cellular heterogeneity, static analyses often obscure the dynamical principles underlying lineage commitment and disease-associated perturbations. The talk will demonstrate how dynamic, systems-level approaches can uncover mechanistic insights that often remain hidden in conventional analyses.

As a first approach, I will show how hematopoietic progenitor differentiation can be analyzed as a prototypical binary fate decision. In this case, lineage transitions are preceded by attractor destabilization characterized by hallmarks of critical transitions in high-dimensional dynamical systems. Correlation-based early-warning indicators identify commitment points prior to phenotypic separation, establishing a quantitative link between Waddington’s landscape metaphor and measurable transcriptional dynamics. Applying this distribution-based framework to large-scale single-cell RNA sequencing data of Parkinson’s disease (PD) patient-based neuronal differentiation reveals accelerated maturation dynamics and altered attractor stability in mutant lines. Thus, the analysis identifies pathway-level perturbations including mitochondrial energetics and protein localization that are partially overlooked by classical differential expression pipelines. Finally, I will show how dynamic signatures from multi-omics characterization can be integrated by non-negative matrix tri-factorization (NMTF). By decomposing gene–cell–condition tensors into interpretable, low-rank modules, NMTF captures coordinated transcriptional programs that correspond to metastable attractors and transitional states indicating disease-relevant regulatory modules across molecular layers, thereby bridging single-cell dynamics with systems-level network integration.

Together, these approaches illustrate the power of dynamic investigations at single-cell resolution: from identifying critical transitions in developmental systems to uncovering altered attractor landscapes in neurodegeneration. By integrating dynamical systems theory, information theory, and matrix factorization, we move toward a mathematical framework capable of dissecting cellular decision-making in both health and disease.

Geometry-dependent FGF4-ERK signalling drives epiblast-primitive endoderm proportioning in a Cellular Potts model of the human blastocyst

Millicent Afrifa Opoku

African Institute for Mathematical Sciences Ghana, Ghana

The second lineage differentiation in the human blastocyst partitions the inner cell mass (ICM) into NANOG-high epiblast (EPI) and GATA6-high primitive endoderm (PrE) populations. Although the FGF4-FGFR-ERK signalling pathway is known to mediate this decision, the quantitative relationship between signalling range, tissue geometry, and the resulting EPI:PrE proportion remains poorly defined in human blastocyst. A Cellular Potts Model (CPM) of blastocyst formation was developed that incorporates a minimal paracrine signalling network coupling FGF4 secretion, diffusion, and ERK-mediated feedback to cell fate dynamics. Each simulated cell contains an internal variable representing its position along the NANOG-GATA6 axis, which evolves according to a stochastic differential equation biased by local ERK activity. The model integrates cell-cell mechanics, diffusion, and feedback interactions to quantify how geometry and FGF4 diffusion range shape lineage proportioning within the ICM. Simulations reproduce key qualitative features observed in human blastoids, including salt-and-pepper distributions and enrichment of PrE-like cells along the cavity interface. Perturbations mimicking MEK inhibition or reduced FGFR activity disrupt PrE differentiation, consistent with experimental observations. These findings demonstrate that local FGF4-ERK coupling within realistic tissue geometry is sufficient to generate robust EPI and PrE proportioning without predefined asymmetry. The model establishes a quantitative framework linking paracrine range, spatial organization, and lineage specification during early human development.

STORMI leverages CRISPR interventions, DNA sequence syntax and multi-lineage dynamics to infer the regulatory mechanisms governing cell state dynamics

Alexander Aivazidis[1], Cameron Smith[2], Tara Chari[3], Stefan Schrod[1], Paul Kaegy[4], Matt Levine[5], Jonathan Kunz[4], Smaran Nair[4], Manu Saraswat[4], Katharina Mikulik[4], Stephanie Manz[4], Alexandra Pettet[6], James Reddington[6], Lars Steinmetz[7], Oliver Stegle[1], Luca Pinello[2]

[1]European Molecular Biology Laboratory, Genome Biology Unit, Heidelberg, Germany; [2]Massachusetts General Hospital Research Institute, Department of Pathology, Harvard Medical School, Boston, MA, USA; [3]The Broad Institute of MIT and Harvard, Eric and Wendy Schmidt Center, Cambridge, MA, USA; [4]German Cancer Research Center (DKFZ), Division of Computational Genomics and Systems Genetics, Heidelberg, Germany; [5]Basis Research Institute, Cambridge, MA, USA; [6]GSK, Heidelberg, Germany; [7]Stanford University School of Medicine, Department of Genetics, USA

Dynamical models are fundamental tools for describing biological systems across various domains. While simulations of coupled ODEs/SDEs are wide-spread, the robust and scalable inference of their parameters from noisy datasets collected at uncertain measurement time points remains an open challenge. To close this gap we present STORMI, a modelling library based in Jax and Numpyro, leveraging amortized Bayesian inference, JIT-compiled numerical ODE/SDE solvers and a modular design to enable creation and inference of dynamical models with unprecedented speed, robustness and flexibility. We demonstrate the use of STORMI on the task of inferring gene regulatory networks (GRNs) from single-cell genomics datasets. Existing methods for this task struggle, because many alternative model structures can explain a given dataset equally well, rendering this a largely non-identifiable problem. New opportunities have emerged with single-cell CRISPR perturbation screens, which combine controlled interventions with multicellular organoid models, multi-omic readouts and profiling across multiple differentiation time points. STORMI's flexibility allows quickly formulating a dynamical model to fit such complex experimental designs and its scalability enables inference on datasets of 100,000s of cells within minutes. First, we illustrate how the empirical parameter identifiability of different STORMI models depends on data features, such as the number of cells, omics modalities, differentiation time points and CRISPR perturbations covered, thus both validating our models and providing a tool to plan optimal experimental designs for GRN inference. Second, we gathered two public and one unpublished CRISPR perturbation screen to benchmark and demonstrate the use of STORMI on real-world data. Our unpublished CRISPR perturbation dataset covers heart-organoids measured at 7 differentiation time points with joint RNA and ATAC readouts and subject to 400 CRISPR perturbations, making this the largest such screen available to date. Unlike previous GRN benchmarks that were based on comparisons to literature curated ground truth labels, we directly assess STORMI on the task of predicting the RNA and ATAC counts of cells at unseen differentiation time points or with unseen CRISPR perturbations (i.e. not included in training data). STORMI links computation and experiment design, machine learning and biophysical modelling in a scalable, extendable library. We provide a blueprint for building increasingly powerful in-silico mathematical models of cellular dynamics and envision further applications across various domains in the mathematical life sciences.

Enhancing epidemiological parameter inference using quantitative diagnostic data

Punya Alahakoon, James Hay

Pandemic Sciences Institute, University of Oxford, UK

Most infectious disease datasets are dichotomous, typically indicating the presence or absence of infection. However, many contain quantitative measurements such as cycle threshold (Ct) values from PCR tests or antibody titers from serological assays. Despite this, epidemiological models often rely on dichotomized data to infer key immunological and transmission parameters. This simplification discards valuable information embedded in the original quantitative measurements. In this work, I will first quantify the information loss incurred by dichotomizing quantitative data using metrics such as the Kullback–Leibler (KL) divergence. I will then present a framework for incorporating quantitative measurements, specifically Ct values and antibody titers, into epidemiological models to better capture population-level dynamics. I will apply this framework to COVID-19 data in the United Kingdom and explore different testing settings and data availability scenarios. Finally, I will discuss the practical considerations and methodological advantages of using quantitative data over dichotomized alternatives, highlighting implications for inference, model accuracy, and public health decision-making.

Adapting Confidence Thresholds and Profile Likelihood Analysis to Small Sample Sizes

Rafael Arutjunjan, Jens Timmer

Institute of Physics, University of Freiburg, Germany

How do we know what is true when our evidence is limited? A reproducibility crisis has made itself increasingly felt over the past two decades, particularly within medicine and the life sciences. While the causes are undoubtedly multifactorial in nature, a major factor contributing to the irreproducibility of previously published results is given by poor or inadequate analysis. Researchers often tacitly make use of the so-called large sample limit assumption, where formulas simplify as the number of data points tends to infinity. One example of this is provided by the confidence thresholds computed for statistical tests, which become lower as the number of data points increases. However, this begs the question of how well the large sample limit assumption actually holds in any given situation. Are 5,000 data points already sufficiently close to infinity for this approximation? What about 200? Using thresholds derived in the large sample limit at small to moderate sample sizes causes many results to be erroneously classified as significant, when they are in fact still below a more appropriately computed threshold. This artificially inflated trust into obtained results contributes directly to the irreproducibility of published findings. Adjusting confidence thresholds for small sample sizes is therefore not just a minor technical correction, but is instead central to maintaining the integrity of scientific claims. We suggest a refined analytical approach for computing confidence thresholds of likelihood ratio tests for data with Gaussian noise of either known or unknown variance. Our approach is based on the F-distribution and explicitly takes into account the number of observed data points and degrees of freedom of the underlying model. We demonstrate that our method results in generally larger confidence thresholds and recovers the well-known χ^2 result from above in the large sample limit as expected. Moreover, by comparing the proposed method against the large sample limit thresholds, we can precisely quantify by how much the correct confidence threshold is underestimated depending on the actual sample size and number of model parameters. We hope this provides convincing evidence that the gain in statistical robustness offered by our method is well worth the slight increase in technical complexity, especially whenever the ratio of data points to model parameters is comparatively small.

Fractional-Order Modelling and Data-Driven Analysis of Lymphatic Filariasis Dynamics in Ghana

Fredrick Asenso Wireko[1], Rebecca Awerigiya[1], Isaac Adu[2], Joshua Nii Martey[3], Bernard Oduoku Bainson[1], Joshua Kiddy Kwasi Asamoah[1]

[1]Kwame Nkrumah University of Science and Technology, Kumasi, Ghana; [2]Kumasi Technical University, Ghana; [3]African Institute of Mathematical Sciences Ghana, Ghana

Lymphatic filariasis (LF) is a chronic vector-borne disease that progresses slowly and exhibits delayed treatment response and long-term persistence in endemic regions. These features introduce memory and hereditary effects that are inadequately captured by conventional integer-order models. To address this limitation, we develop a fractional-order deterministic model of LF transmission using the Caputo derivative to incorporate the non-local memory property of the infection process. Analytical investigations establish the positivity, boundedness, and uniqueness of the model solutions. The basic reproduction number, derived through the next-generation matrix method, is $R_0 = 1.5746$, indicating endemic persistence in the absence of control measures. Model parameters were estimated by fitting to LF incidence data from Ghana (2010–2021), achieving a normalized mean square error of 0.0198, demonstrating excellent consistency between simulated and observed data. Sensitivity analysis based on partial rank correlation coefficients (PRCCs) identified the mosquito biting rate (β) as the most influential parameter driving transmission (PRCC = 0.83), while the awareness rate (κ) and treatment rate (β_2) had strong negative effects (PRCC = −0.71 and −0.65, respectively). These findings emphasize that interventions targeting awareness and drug coverage are critical for reducing LF burden. Numerical simulations performed for fractional orders $0.80 \leq \varrho \leq 1$ demonstrate that decreasing ϱ significantly alters the disease trajectory. Lower values of ϱ delay epidemic decay, extend infection persistence, and damp transient oscillations, clear indicators of memory-driven dynamics. The fractional-order framework captures how historical infection and treatment states influence present outcomes, unlike classical integer-order models that assume instantaneous responses.

Mechanochemical Energy Landscapes Under Force: Catch–Slip Bonds in T-Cell Activation

Yogesh Bali, Alan Rendall

Johannes Gutenberg University of Mainz, Germany

Traditional theories explain T-cell activation by antigen concentration, binding affinity, and dissociation rate, but they fail to account for its extraordinary sensitivity.[1] Recent cryo-electron microscopy and single-molecule studies implicate mechanical load transmitted through the TCR-pMHC-CD3 axis in promoting signaling.[2] We develop a minimal mechanochemical energy-landscape model that links force to changes in activation barriers and bond lifetimes. Our aim is a compact, testable bridge between force, landscape topology, and T-cell activation. Methodologically, we couple a mechanochemistry framework with Newton-trajectory analysis to track force-driven state changes, compute force-dependent barriers, and map them to lifetimes via Kramers–Langer theory.[3,4] Applied across peptide classes, the model reproduces a clear pattern: agonists and weak agonists display catch--slip behavior---with stability peaking at intermediate load---whereas antagonists show pure slip with monotonic weakening, consistent with recent catch-bond modeling of TCR signaling.[5] Our framework provides a testable mechanochemical link between force, barriers, and lifetimes in TCR recognition and a path to refine predictions with targeted measurements for T-cell signaling under load.

References

1. Huang J, Brameshuber M, Zeng X, et al. A single peptide-major histocompatibility complex ligand triggers digital cytokine secretion in CD4(+) T cells. *Immunity*. 2013;39(5):846-857. doi:10.1016/j.immuni.2013.08.036
2. Dong D, Zheng L, Lin J, et al. Structural basis of assembly of the human T cell receptor-CD3 complex. *Nature*. 2019;573(7775):546-552. doi:10.1038/s41586-019-1537-0
3. Quapp W, Bofill JM, Ribas-Ariño J. Toward a theory of mechanochemistry: Simple models from the very beginnings. *Int J Quantum Chem*. 2018;118:e25775. doi:10.1002/qua.25775
4. Langer SJ. Statistical theory of the decay of metastable states. *Ann. Phys*. 1969;54(2):258-275. doi:10.1016/0003-4916(69)90153-5
5. Choi HK, Cong P, Ge C, et al. Catch bond models may explain how force amplifies TCR signaling and antigen discrimination. *Nat Commun*. 2023;14(1):2616. doi:10.1038/s41467-023-38267-1

.

A Fractional Derivative Approach to Model Anomalous Mass Transport in Atherosclerosis Plaque Formation

Francis Tetteh Batsa

Kwame Nkrumah University of Science and Technology, Kumasi, Ghana

Introduction and Motivation: Atherosclerosis, initiated by LDL accumulation in the arterial intima,[1] is governed by mass transport kinetics within the wall's complex, porous microstructure. Classical PDE models fail to capture the observed chronic, slow-penetration behaviour due to the tissue's heterogeneous, viscoelastic nature, which introduces significant non-local and temporal memory effects. A physically realistic framework is required to model this anomalous transport. Methodology: This work presents a novel mathematical model for LDL transport utilising fractional calculus. The arterial wall is treated as a porous medium.[2] Governing macro-scale transport equations are rigorously derived using the Method of Volume Averaging (MVA).[3] Crucially, we employ advanced fractional operators: the Atangana-Baleanu derivative ($\mathcal{D}_t^{\alpha}$) in time (modelling viscoelastic memory) and the Riesz derivative ($\mathcal{D}_x^{\beta}$) in space (capturing spatial non-locality/anomalous diffusion). The fractional orders $\alpha \in (0,1]$ and $\beta \in (1,2]$ serve as quantifiable metrics for the degrees of anomalous transport. The resulting FPDE is solved using advanced finite difference techniques. Results and Discussion: Comparative analysis shows the fractional model achieves a superior fit to experimental LDL concentration data, validating the inclusion of non-local effects. The FPDE model strongly aligns with clinical observations, including accelerated accumulation under hypertension conditions. The formulation accurately simulates the sub-diffusive, long-time-scale penetration of LDL. Sensitivity analysis demonstrates that the fractional orders provide realistic physiological parameterisation. Specifically, the model establishes a more accurate link between Wall Shear Stress (WSS) and LDL accumulation than classical models, accurately predicting focal accumulation and plaque susceptibility in low-WSS regions. Conclusion and Significance: The deployment of fractional calculus provides a fundamentally improved mathematical framework for studying mass transport in atherosclerosis, offering enhanced predictive power for early lesion development and a superior mechanistic understanding. By quantifying the anomalous transport, the model is a powerful tool for refining diagnostic and prognostic models of cardiovascular risk.

1. Wang Y, Wang X, Wang C, Zhou J. Global, Regional, and National Burden of Cardiovascular Disease, 1990-2021: Results From the 2021 Global Burden of Disease Study. *Cureus.* 2024;16(11):e74333. doi:10.7759/cureus.74333
2. Vafai K. Porous media: Applications in biological systems and biotechnology (1st ed.). *CRC Press.* 2010. doi:10.1201/9781420065428
3. Whitaker S. (2013). The Method of Volume Averaging. Springer. 2013.
4. Wada S, Karino T. Computational study on LDL transfer from flowing blood to arterial walls. *In: Clinical Application of Computational Mechanics to the Cardiovascular System (pp. 157–173). Springer*. 2000. doi:10.1007/978-4-431-67921-9_16.

Inference from Phylogenetic Somatic Variant Trees

Nils Becker

German Cancer Research Center, Heidelberg, Germany

Whole Genome deep sequencing (WGS) now allows us to comprehensively profile genetic variants arising in somatic cell populations. Starting from individual cells sampled from a target tissue followed by clonal expansion in culture, WGS can be used to establish phylogenetic trees depicting the clonal evolution of the tissue. Sampled cells are at the leaves of such variant trees, and internal nodes are inferred as the common ancestors of clades of related cells via variants sharing across cells. Classical phylogenetics allows inference of effective population sizes along the history of variant trees. However, relating molecular time and actual time, and rigorous inference of the underlying dynamics of the cell population remains challenging. I present a framework for parameter estimation from variant trees generated by possibly time-dependent birth-death processes. Drawing from recent advances in the theory of branching processes, the pronounced effects of time-dependent dynamical rates and of sparse sampling are accounted for exactly.

Quantitative Modeling Reveals Feedback Control of T Cell Receptor Trafficking and Surface Homeostasis

Simon Beyer[1,2], Claudia Juraske[2,3,4,5,6], Sara Hartmann[2,3,4,5,6], Anna Morath[2,3,5,6], Deniz Saltukoglu[2,3,5], Michael Reth[2,3,5], Jens Timmer[1], Viviane Timmermann[1,7], Wolfgang W. Schamel[2,3,4,5,6]

[1]Institute of Physics, Faculty of Physics and Mathematics, University of Freiburg, Freiburg, Germany; [2]CIBSS Centre for Integrative Biological Signalling Studies, University of Freiburg, Freiburg, Germany; [3]BIOSS Centre for Biological Signalling Studies, University of Freiburg, Freiburg, Germany; [4]Faculty of Biology, University of Freiburg, Germany; [5]Spemann Graduate School of Biology and Medicine (SGBM), University of Freiburg, Germany; [6]Centre for Chronic Immunodeficiency (CCI) and Centre for Cell and Gene Therapy Freiburg (CGF), Faculty of Medicine, University Clinics Freiburg, Freiburg, Germany; [7]Institute for Molecular Medicine and Cell Research, Faculty of Medicine, University Clinics Freiburg, Freiburg, Germany

The dynamic regulation of T cell receptor (TCR) surface expression ensures that T cells remain responsive to their cognate antigens. Maintaining constant TCR surface levels is essential for preserving antigen sensitivity and ensuring appropriate cell responsiveness upon activation. However, TCR abundance is subject to fluctuations arising from cellular processes such as proliferation, differentiation, and activation-induced internalization. Experimental data indicate that TCR assembly is finalized post endoplasmic reticulum (ER), likely in the Golgi, and that synchronous release of intracellularly retained TCR complexes results in a transient overshoot at the cell surface, which equilibrates over time. To quantitatively characterize these dynamics, we developed an ordinary differential equation model to describe TCR synthesis, assembly, trafficking, and feedback control of ER-to-cell surface transport. Model calibration was performed using maximum-likelihood estimation with an L1 regularization term to identify the minimal set of feedback mechanisms consistent with the experimental observations. Subsequently, profile likelihood analyses were used to assess parameter identifiability and quantify prediction uncertainties. This combined modeling and experimental approach supports the existence of a negative feedback of surface TCRs acting on ER export, which might be mediated by ligand-independent basal signaling, that regulates TCR surface levels following perturbations. This mechanism may allow T cells to maintain a stable pool of functional receptors across cell divisions and activation cycles, thereby ensuring readiness for antigen recognition within the adaptive immune response.

Modelling the Spread of Healthcare-Associated Infections through a Nationwide Patient-Based Network in France's Healthcare Settings

Shrichand Bhuria, Pascal Crépey

EHESP Rennes, France

Background: Hospital networks—formed through the movement of patients within and between healthcare facilities—create complex webs of connections that act as critical pathways for the transmission of hospital-acquired infections (HAIs). While inter-hospital pathogen spread has been widely studied using aggregate transfer data, the finer-scale dynamics of transmission remain poorly understood. In particular, the role of direct patient-to-patient co-presence within and between hospitals—and how these shape real-world transmission pathways across a national hospital network—has not been adequately explored. Objective: We reconstruct a high-resolution patient contact network of the French healthcare system to investigate hidden transmission pathways of HAIs and antibiotic-resistant bacteria (ARB) colonization. We address three key questions: (i) How is colonization risk distributed spatially across France, based on patients' residence and hospitalization locations? (ii) How does the geographic origin of an outbreak influence the speed and extent of nationwide spread? (iii) Which individual (patient)- and hospital-level characteristics are the strongest drivers of colonization risk? Methods: We use the 2023 PMSI-MCO hospital discharge database, covering over 30 million admissions from all public and private hospitals across metropolitan France (96 departments). We construct a patient-based network (PBN) of 4.08 million patients and more than 1,500 hospitals, linked via over 96 million weighted edges representing overlapping overnight stays within the same hospital wards. To simulate pathogen spread, we implement a stochastic Susceptible–Infected (SI) model over 365 day-by-day contact networks. The SI model was chosen for its simplicity and suitability for large, complex networks, focusing on reachability without assuming pathogen-specific parameters or recovery periods. Each simulation began on a randomly selected calendar day and cycled through the full year to avoid outbreak timing bias. A generalized additive model (GAM) regression identified key predictors of colonization risk at both patient and hospital levels. Key Findings: The PBN exhibits a heterogeneous but non–scale-free structure with a lognormal degree distribution, indicating that transmission chains are driven by moderately connected patients rather than super-spreaders. Spatial mapping of colonization risk revealed distinct clusters of elevated risk across France. High-risk zones were not confined to densely populated urban areas—several rural regions also exhibited high risk—while some urban areas showed low risk, suggesting that population density is not a dominant predictor of infection risk. Hospital-level spatial risk maps revealed strong heterogeneity, and ward-level colonization risk was also non-uniform, underscoring the need for ward-specific infection control strategies. Using the GAM model, we identified major determinants of colonization risk at both the patient level (e.g., demographics, number of admissions, length of stay, number of wards or hospitals visited, delay between readmissions) and the hospital level (e.g., total admissions, number of ward types, average length of stay, hospital degree). Conclusion: This study presents the first nationwide, dynamic reconstruction of a real-world patient contact network to model HAI transmission across the French healthcare system. The PBN framework reveals how HAIs propagate through hospital networks and extend into the community via discharged patients, providing spatial patterns of colonization risk highly relevant for public health surveillance. By identifying wards with higher colonization risk, this approach supports targeted infection-prevention strategies. Its pathogen-agnostic design makes it broadly applicable to diverse resistant organisms and suitable for both regional and national surveillance within complex healthcare networks.

A hybrid approach for the simulation of spatially-resolved susceptible-infected-recovered epidemics using the method of moments for stochastic reaction networks

Julia Bicker

German Aerospace Center, Cologne, Germany

Stochastic reaction networks have been widely used to study biochemical reaction systems. The temporal evolution of such systems is governed by the Chemical Master Equation (CME) whose solution is a time-dependent probability distribution on all possible system states. However, with a large number of particles and reactions, the system state rapidly becomes intractable, rendering the CME practically unsolvable in most realistic scenarios. To study the system's behavior despite this intractability, stochastic simulation algorithms can be used to generate sample trajectories of the underlying stochastic process. Yet, since a multitude of simulations is required to obtain a reliable approximation of the full probability distribution, this can quickly become a computationally expensive task. An alternative is the Method of Moments, which involves the derivation of moment equations describing the dynamics of the mean and all central moments of the CME through a system of ordinary differential equations. This method is particularly useful for systems exhibiting large stochasticity. However, as lower-order moments generally depend on higher-order moments, moment closure methods are necessary. Such closure methods approximate higher-order moments in terms of lower ones, inevitably introducing a trade-off between accuracy and computational efficiency. Mathematical epidemiological models have long been used to study transmission dynamics of infectious diseases and support public health decision-making. These models range from deterministic mean-field models assuming a homogeneously mixed population, to metapopulation models accounting for spatial heterogeneity, and detailed agent-based models. In this work, we apply stochastic reaction networks in an epidemiological context. Specifically, we present a spatially-resolved stochastic susceptible-infected-recovered epidemiological model with different regions, where the movement of individuals between regions influences the local and global infection dynamics. We derive the corresponding system of moment equations and investigate the performance of zero-cumulant closure under varying conditions. To balance computational cost and the accurate representation of stochastic effects, we propose a hybrid modeling approach that combines stochastic simulation with moment-equation-based approximation. We analyze different switching criteria used to transition between the stochastic and deterministic components of the hybrid model, comparing their errors in means and variances in relation to the computational effort. Furthermore, we demonstrate that the hybrid approach is able to accurately capture the system's stochastic dynamics in regimes where the naive moment closure approach fails.

Influence of Culture Media Composition on Drug Sensitivity in CRC organoids

Jasmitha Boovadira Poonacha

LIMES Institute, University of Bonn, Germany

Background: Colorectal cancer (CRC) is the third most common and deadliest cancer worldwide. Despite recent advancements, our understanding remains limited, and new effective treatments are urgently needed. While culture-based studies of cancer cells are common, few have explored how different metabolites in culture media influence drug response, which could be crucial for cancer research. Method: A biobank of tumor and matched normal colonic organoid lines was established from untreated CRC patient samples. The organoids were cultured in various physiological and non-physiological media. Compound sensitivities were determined in a semi-automated manner using CellTiter-Glo. The IC50 and GR50 values were determined using logarithmic (inhibitor)-response curves, wherein GR50 values reflect growth rate-independent compound sensitivities. Results: A significant influence of culture media on drug response was observed among different media within the same patient-derived organoid (PDO) cultures. The sensitivities of few standard-of-care antimetabolites like 5-Fluorouracil (5-FU) demonstrated notably greater responsiveness in physiological media, such as Human Plasma-Like Media (HPLM)), this effect was highly patient-dependent.The potential underlying basis for this enhanced responsiveness was examined in relation to metabolic parameters, including uric acid and glucose concentrations. Conclusion: This study highlights the essential role of culture media in shaping organoid drug sensitivity, a factor that may critically influence the translational potential of organoid-based research.

On a modified Leslie-Gower Model with Prey Defense and Predator Cannibalism

Eric Takyi[1], Gloria Agyeiwaa Botchway[2]

[1]Ursinus College, Collegeville, PA, USA; [2]University of Ghana, Department of Mathematics, Legon, Accra, Ghana

Recent experiments show that cannibalism in predators and defense in prey can both occur concurrently. Motivated by this, we investigate a predator-prey system where cannibalism occurs in predators and defense in prey simultaneously. System analysis shows that depending on the prey defense and predator cannibalism parameters, respectively, one can have global stability of the coexistence and prey free states, bi-stability dynamics or up to three interior equilibria. Local stability analysis shows that the combined effects of prey defense and predator cannibalism cannot drive both populations to extinction and for some parameter choices, can destabilize the system. The system undergoes standard co-dimension one bifurcations, including Hopf bifurcation, transcritical bifurcation and saddle-node bifurcation. We support our theoretical results with numerical experiments and discuss their ecological implications.

Inferring Cell-Cell Dynamics from Cell Trajectory Data Using Deep Attention Networks, and the Mechanisms Underlying T Cell Behavioural Heterogeneity in the Response to Cancer

James Boyle[1], Veronika Pfannenstill[2], Jacky Ko[2], Ruth Baker[1], Helen Byrne[1]

[1]Oxford Mathematical Institute, University of Oxford, UK; [2]Kennedy Institute of Rheumatology, University of Oxford, UK

Cell movement is an important component of many biological processes, including collective cell migration and the immune response to cancer. In many systems interactions between nearby cells are a key driver of cell movement, yet it can be difficult to infer and express the rules governing cell-cell interactions in a manner that is biologically accurate and interpretable. Here we present a model, based on the theory of deep attention networks, that learns how cell-cell interactions affect cell movement directly from cell trajectory data. We develop a suite of tools that leverage the structure of this model to present the learned interaction dynamics in an interpretable manner. Our model extends previous work in this area, providing deeper insights into cell-cell interaction dynamics, moving beyond inferring simply whether cells interact to how these interactions affect cell movement, and providing the ability infer cell-cell interaction dynamics in multi-type cell movement systems. We use our model to infer the rules governing the collective migration of kidney epithelial cells, and to understand how cytotoxic T cells and tumour cells interact in an in vitro co-culture. We then use these results to build an agent based mathematical model of the T cell response to cancer. Recent experimental studies have observed significant variability in the empirical killing capabilities of cytotoxic T cells - that is, some T cells are observed to be much more prolific killers of cancer cells than others. We use our mathematical model to investigate what mechanisms might give rise to this observed heterogeneity, and ask whether it can be explained by a model in which all T cells follow the same behavioural rules.

Mechanistical modelling of C4 plants - hydraulics model

Jonas Braß, Jérémie Prokob, Julia-Sarita Brand, Antonio Rigueiro-Mesejo, Chilperic Armel Foko Kuate, Martin Lercher

Institute for Computer Science and Department of Biology, Heinrich Heine University, Düsseldorf, Germany

C4 photosynthesis is one of the three major photosynthetic pathways which distinguishes itself from the other by spatial separation of car- bon fixation and sugar production. Although only present in about 3% of all plant species C4 photosynthesis is responsible for roughly 25% of global carbon fixation. In addition, plants utilizing C4 photosynthesis thrive under harsh con- ditions (such as high temperature, low water availability and low atmospheric CO2 concentration). This makes the C4 pathway a prime candidate for crop engineering. To utilize its adaptability, we aim at a deeper understanding of its properties and reactions to environmental conditions. There already exist a multitude of predictive models which are used to understand singular aspects of plants. Those models are often too specific and focus only on singular aspects of plant processes (e.g. von Caemmerer model for C4 biochemistry or De Swaef model of soil-plant-atmosphere continuum). While those models are reductionist we aim at a holistic description of the C4 photosynthesis. With this approach we intend to better understand certain traits of a C4 plant, its use of water and energy as well as its interaction with the environment (e.g. how C4 will thrive in specific climate conditions). This model then will enable us to do a deeper analysis of C4 plants such as spatial compartment configura- tions that are currently not reachable. This should advance our understanding for C4 plants (e.g. their adaptation to their environment). In addition we study C4 evolution using Rubisco assimilation rate as a proxy for fitness. Using empirical environmental data and an early implementation of the hydraulics model we show initial results and talk about challenges and future steps to improve the model.

Heterogeneity in temporally fluctuating environments

Alexander Browning[1], Sara Hamis[2]

[1]University of Melbourne, Australia; [2]Uppsala University, Sweden

Many biological systems regulate phenotypic heterogeneity as a fitness-maximising strategy in uncertain and dynamic environments. Analysis of such strategies is typically confined both to a discrete set of environmental conditions, and to a discrete (often binary) set of phenotypes specialised to each condition. In this talk, we extend on both fronts to encapsulate both a discrete and continuous spectrum of phenotypes arising in response to two broad classes of environmental fluctuations that drive changes in the phenotype-dependent growth rates. We present a series of analytical and semi-analytical results that reveal regimes in which both discrete and continuous phenotypic heterogeneity is evolutionary advantageous.

Virtual Embryo: Blastocyst and Organoid Models in the Morpheus Simulation Framework

Lutz Brusch, Diego Jahn, Jörn Starruß

Technische Universität Dresden, Germany

Multicellular models integrating cell-cell signaling, gene regulation, proliferation and tissue mechanics are needed to unravel the organizational principles of embryo morphogenesis. We apply the open-source simulation framework Morpheus to such multicellular models.[1] We analyze how cells dynamically polarize and differentiate in response to signals from their environment. This allows to simulate mouse blastocyst development from the zygote to the 128-cell stage.[2] We then couple this multicellular model to a fluid transport model and study amniotic cavity formation in a human embryoid model. From a methods perspective, Morpheus keeps the model definition strictly separated from the simulation code. It uses the domain-specific language MorpheusML to define multicellular models in a modular manner through a user-friendly GUI.[3] A numerical simulation is then composed by parsing the MorpheusML model definition and automatic scheduling of predefined components in the simulator. This Morpheus simulation framework and FAIR MorpheusML model repository enable collaborative workflows.[4]

1. Morpheus homepage: https://morpheus.gitlab.io
2. Cang Z, Wang Q, Wang, Q et al. Blastocyst Development. https://identifiers.org/morpheus/M9999
3. MorpheusML language: https://doi.org/10.25504/FAIRsharing.78b6a6
4. Model repository: https://morpheus.gitlab.io/models

Emergent dynamics of cellular decision making in multi-node mutually repressive regulatory networks

Harshavardhan BV[1], Hanuma Sai Billakurthi[1], Sarah Adigwe[2], Kishore Hari[3], Herbert Levine[3], Tomas Gedeon[2#], Mohit Kumar Jolly[1#]

[1]Indian Institute of Science, Bengaluru, India; [2]Montana State University, Bozeman, USA; [3]Northeastern University, Boston, USA

[#]shared last authorship

Stem cell differentiation during development is governed by the dynamics of the underlying gene regulatory networks (GRNs). Mutually inhibiting nodes/collection of nodes encompass the GRNs that govern differentiation to two distinct fates. However, the properties of GRNs that can allow differentiation into n-terminal phenotypes are poorly understood. In this study, we examine toggle-n networks, encompassing mutual inhibitions among multiple transcription factors (TFs), to derive generalized insights regarding the dynamics underlying differentiation into n-terminal phenotypes. We show through numerical and analytical methods that steady-state distributions of these networks involve co-expression of multiple cell state-specific TFs, indicating the presence of multi-potent hybrid phenotypes during multi-lineage differentiation. Furthermore, incorporating a case study of T-helper cell differentiation, we show that cytokine signalling and specific asymmetry of regulatory links can drive further directed differentiation of these hybrid phenotypes into particular cell states within our mathematical framework.

Creating Realistic and Controllable Synthetic Tumor Microenvironment Images Using Diffusion Models Conditioned on Simulation Images

David Cicchetti, Johannes Textor, Inge Wortel[#], Tom Claassen[#]

Radboud University, Nijmegen, The Netherlands

[#]shared last authorship

Motivation: Understanding the tumor microenvironment (TME) is a challenging task due to its complex and dynamic nature and the presence and interactions of many different cell types, but is critical for e.g. developing immunotherapy.[1,2] A method to generate high-quality synthetic TME data could facilitate TME research e.g. by providing annotated data for machine learning or by facilitating power planning.[3] One approach to generate synthetic TME images is through simulation models, which provide high control over the tumor environment and cell configuration,[4] but yield images that are visually simplistic compared to real-world images. Conversely, foundation models can be used to generate highly realistic images,[5] but lack exact control over cell configurations. Therefore, we propose a conditional diffusion model which uses an image (from e.g. a simulation) as a conditioning signal for AI-generated microscopy images while preserving control over cell configurations. Methods: We use a latent diffusion model as introduced by Rombach et al. with images as a conditioning signal and train on multiplex-immunohistochemistry data.[6] The conditioning image y contains $3 * \mathrm{n}$ channels, with n the number of cell types, using one channel each to represent the membrane, cytoplasm, and nucleus segmentations of the cells of that type. Additionally, we can add other background artifacts such as tumor tissue segmentations as another channel. We use an available pre-trained autoencoder network (encoder $\mathcal{E}$ and decoder $\mathcal{D}$) to transform our images x into latent space ($\mathrm{z} = \mathcal{E}(\mathrm{x})$) and back. Then we train a Denoising Diffusion Probabilistic Model (DDPM), which consists of a U-Net (ϵ_θ) and the conditioning network τ_θ, at different times t of the diffusion process with the loss $\mathrm{E}_{\mathcal{E}(\mathrm{x}),\mathrm{y},\epsilon\sim\mathcal{N}(0,1),\mathrm{t}}\left[\left|\left|\epsilon - \epsilon_\theta\left(\mathrm{z_t},\mathrm{t},\tau_\theta(\mathrm{y})\right)\right|\right|_2^2\right]$. Furthermore, we perform an ablation study comparing different conditioning signals, and compare the Latent Diffusion to a CycleGAN approach. Results: To evaluate our model, we created consistency metrics to assess the level of control over cell configurations in generated images we find that our model performs very well in this area: compared to the conditioning signal, less than 0.05% of cells are hallucinated, less than 0.4% of cells disappear, less than 4% of cells are merged, less than 1% of cells split and less than 2% of cells are attributed to the wrong cell type. In addition, we check the image realism both visually and using Frechet Inception Distance (FID) and Clip Maximum Mean Discrepancy (CMMD). We find that our conditioning approach yields visually realistic images, supported by relatively low scores (FID: ~6, CMMD:~0.5) , although still higher than distances between the test and validation sets of real images (FID:~3.4, CMMD:~0.001). Lastly, we show how our synthetic TME images can be used in conducting a power analysis, similar to Baker et al.,[3] to estimate the T cell infiltration rate into tumors. Discussion: Since our method allows us to generate lots of data by transforming simulation images (from e.g. a CPM) with high consistency, we can easily create a supervised training pipeline to fine-tune existing segmentation models on difficult datasets. In addition, we believe this method can be used to conduct power analyses for estimating cell parameters from (microscopy) images.

References:

1. Sadeghi Rad H, Monkman J, Warkiani ME, et al. Understanding the tumor microenvironment for effective immunotherapy. *Med Res Rev*. 2021;41(3):1474-1498. doi:10.1002/med.21765

2. Vasaturo A, Halilovic A, Bol KF, et al. T-cell Landscape in a Primary Melanoma Predicts the Survival of Patients with Metastatic Disease after Their Treatment with Dendritic Cell Vaccines. *Cancer Res*. 2016;76(12):3496-3506. doi:10.1158/0008-5472.CAN-15-3211
3. Baker EAG, Schapiro D, Dumitrascu B, Vickovic S, Regev A. In silico tissue generation and power analysis for spatial omics. *Nat Methods*. 2023;20(3):424-431. doi:10.1038/s41592-023-01766-6
4. Mahlbacher G, Curtis LT, Lowengrub J, Frieboes HB. Mathematical modeling of tumor-associated macrophage interactions with the cancer microenvironment. *J Immunother Cancer.* 2018;6(1):10. 30. doi:10.1186/s40425-017-0313-7
5. Ding T, Wagner SJ, Song AH, et al. A multimodal whole-slide foundation model for pathology*. Nat Med*. 2025;31(11):3749-3761. doi:10.1038/s41591-025-03982-3
6. Rombach R, Blattmann A, Lorenz D, Esser P, Ommer B. High-Resolution Image Synthesis with Latent Diffusion Models. arXiv. 2022. doi:10.48550/arXiv.2112.10752

Investigating endogenous opioids unravels the mechanisms behind opioid induced constipation, a mathematical modeling approach

Celvic Coomber[1,2], Vikram Sunkara[2,3,4]

[1]TU Berlin, Germany; [2]Zuse Institute Berlin, Germany; [3]FU Berlin, Germany; [4]German Rheumatology Research Center, Berlin, Germany

Endogeneous opioids, such as Endomorphin-2, are not typically associated with severe constipation, unlike pharmaceutical opioids, which induce opioid-induced constipation (OIC) by activating μ-opioid receptors in the gastrointestinal tract. In this study, we present a mathematical model, which integrates the serotonergic and opioid pathways, simulating the interaction between serotonin and opioid signaling within the enteric nervous system (ENS). The model explores the mechanisms underlying OIC, with a focus on the change in adenylyl cyclase (AC) activity, cAMP accumulation, and the distinct functionalities of Endomorphin-2 compared to commonly used pharmaceutical opioids. We study the effects of Morphine, Fentanyl, Methadone and contrast them with Endomorphin-2. Our findings reveal that opioids do not perturb the signalling of Serotonin, but only the activity of AC, suggesting that Serotonin levels have no influence in improving opioid-induced constipation. Furthermore, the study reveals that the primary difference between endogeneous and pharmaceutical opioids is their degradation rates. This finding shows that modulating opioid degradation rates significantly improves cAMP recovery. In conclusion, our insights steers towards exploring opioid degrading enzymes, localised to the gut, as a strategy for mitigating OIC.

An Interdisciplinary Approach to Quantifying the Impact of T-Cell Exhaustion on the Tumour Microenvironment

Luke De Bretton-Gordon

Mathematics Institute, The University of Oxford, UK

Understanding the interactions between agents in the tumour microenvironment (TME) is central to improving immunotherapeutic strategies. T-cell exhaustion - characterised by a progressive loss of effector function due to chronic antigen exposure – is thought to play a key role in shaping tumour-immune dynamics. This project, an interdisciplinary collaboration between the Baker, Byrne and Fritzsche groups, aims to combine mathematical modelling, data driven inference, and novel experimental design to investigate how T-cell exhaustion influences tumour growth and spatial organisation. We explore the use of biologically informed neural networks (BINNs) as a framework through which we can learn interpretable mechanistic models directly from experimental data. By integrating neural networks with biologically motivated partial differential equation models, we aim to infer functional forms of cell specific interaction kernels that govern proliferation, migration, and competition between immune and tumour cells. To validate these methods, we first generate and analyse synthetic datasets that mimic key features of experimental observations. These approaches will ultimately be applied to high resolution imaging data quantifying the spatial distribution of specific and non-specific T-cells and tumour cells, both in isolation and in co-culture. This project aims to explore our ability extract mechanistic understanding from complex biological data, bridging experimental and theoretical perspectives to better characterise immune-tumour interactions in cancer.

Condition-Specific Profile Likelihood Analysis: Visualizing how Individual Experimental Conditions Shape Parameter Estimates

Sophia Dehnen[1], Rafael Arutjunjan[1,2,3], Jens Timmer[1,2,3]

[1]Physics Department, University of Freiburg, Germany; [2]Freiburg Center for Data Analysis and Modeling, Freiburg, Germany; [3]CIBSS Centre for Integrative Biological Signalling Studies Freiburg, Germany

In the life sciences and beyond, profile likelihood analysis is a well-established method for assessing parameter identifiability and performing uncertainty quantification in mechanistic non-linear models. By fixing individual parameters of interest to specific test values and re-optimising all remaining parameters, the profile likelihood quantifies the best possible fit to the given data which could still be achieved by the model, if the fixed parameter estimate hypothetically corresponded to the true values. In practice, the observed data used to calibrate a model are typically not generated by just one single experiment, but rather many experiments conducted under different experimental conditions. As a result, parameter estimates often exhibit discrepancies between different datasets for some parameters. Intuitively this means, one condition may favour a large, while another favours a small parameter estimate. A possible naive approach would be to analyse every condition independently and to compare their separately calculated profile likelihoods. However, this quickly becomes computationally very expensive for large numbers of conditions. Moreover, it fails to account for the fact that in many cases, not all conditions contribute information towards all parameters. Instead, our proposed approach is to compute the profile likelihood for all conditions combined and then to decompose it into its condition-specific contributions afterwards. Since the profile paths of the collective profile likelihood are reused in this decomposition, its computational cost is essentially negligible compared to the profile likelihood analysis itself. Despite its computational efficiency, it nevertheless becomes difficult to visually scan the resulting contributions of all conditions for possible inconsistencies when many conditions are involved. For this reason, we also developed a heuristic profile filtering approach that quantifies discrepancies between condition-specific contributions to the profile likelihood of a given parameter. We exemplify our approach using several models from the benchmark collection, defined in the standardised PEtab data format. We demonstrate that our method offers a powerful tool for identifying and assessing potential discrepancies and understanding how specific experimental conditions shape parameter space. Identifying such inconsistencies is especially important during the model development stage.

Spatially Resolved Transcriptomics Reveals Microenvironment-Driven Heterogeneity in Cutaneous T-Cell Lymphoma

Alireza Dostmohammadi

Department of Bioinformatics and Computational Biophysics, Faculty of Biology and Centre for Medical Biotechnology (ZMB), University of Duisburg-Essen, Essen, Germany

Cutaneous T cell Lymphoma (CTCL) is a non-Hodgkin's lymphoma driven by uncontrolled proliferation of skin-resident T lymphocytes. Its most common subtypes are Mycosis fungoides (MF) and Sézary syndrome (SS), with MF comprising ~60% of cases. Although rare, CTCL incidence is rising, ~6.4/million, with diagnosis typically in the mid-50s. Ten-year survival approaches 95% in early disease but falls to ~18% in advanced stages. Early diagnosis remains difficult because CTCL often mimics benign inflammatory skin disorders, and despite substantial research, its mechanisms are not fully understood. Emerging evidence suggests that interactions within the tumor microenvironment (TME) play an important role in CTCL development and progression. To investigate how spatial neighborhood-specific patterns in the TME influence inflammation and CTCL progression, we analyzed spatially resolved transcriptomic data from 95 advanced-stage MF and SS samples and 15 inflamed, non-malignant skin samples across several tissue region types classified by a semi-supervised machine learning approach. As the first upstream classification step, we developed a pipeline that uses matched histopathology to annotate Visium spots into user-defined TME region types and to construct a feature framework using pairwise differential gene expression between these types. Using the resulting features, we trained a logistic regression model to characterize spot-type–specific transcriptional patterns. Applied to our dataset, the model achieved at least 70% accuracy across all spot types on unseen samples and identified distinct gene patterns for each type. The resulting annotation was then used to investigate the spatially resolved patterns of gene expression between TME region types. Spatial transcriptomic data can be produced using sequencing-based, probe-based, imaging-based, and image-guided single-cell RNA sequencing technologies. Among these, 10x Visium and its higher-resolution successor, Visium HD, are the most widely used. Although Visium offers lower spatial resolution, it provides broader tissue coverage, higher RNA capture per spot, and reduced gene-expression sparsity. These properties lead to more stable input features for machine and deep learning applications and enable the inclusion of multiple tissue cores per run, enhancing biological heterogeneity and patient representation for improved model generalization. Moreover, the higher RNA capture per spot provides more comprehensive transcriptomic profiles that can reveal broader expression patterns in downstream analyses, including neighborhood effects. However, many computational approaches for spatial analysis, such as neighborhood-environment analysis, were originally developed for Visium HD data and are not directly compatible with Visium. To fill this gap and to address the limitations while leveraging Visium's advantages, we developed a neighborhood-modeling pipeline for detecting neighbor-dependent gene expression variations based on our complementary pipeline for spot classification. Our neighborhood-dependent modeling component quantifies how the spatial TME structure influences gene expression. The pipeline builds neighborhood graphs and performs permutation testing to identify genes whose expression differs between spots adjacent to a specific neighboring type and non-adjacent spots of the same type. Applied to our dataset, this approach revealed neighborhood-dependent expression shifts, which were consistently stronger in CTCL than in inflamed skin. CTCL tissues show stronger effects of neighboring regions on gene expression, particularly involving dermal and infiltrated areas. Overall, our integrative method for TME region classification plus neighborhood and expression-pattern modeling for Visium spatial transcriptomics in CTCL demonstrates the potential of computational approaches to detect spatially resolved variations in the TME transcriptional landscape even for a rare disease.

Growth Mechanics and the oscillatory biomass allocation in self-replicating cells

Hugo Dourado[1], Martin Lercher[1], Wolfram Liebermeister[2]

[1]Heinrich Heine University, Düsseldorf, Germany; [2]Université Paris-Saclay, INRAE, France

Unicellular organisms adapt to their environments on longer time scales through genetic changes, and on shorter time scales through changes in their biomass composition. Some unicellular organisms, such as yeast, exhibit oscillatory biomass composition even in static growth media, but the possible function of these oscillations has not yet been fully clarified. Here we show that the best possible strategy for self-replicating cells to maximize their fitness is indeed to allocate their biomass in an oscillatory manner, even if the exact regulatory or passive mechanisms underlying this behavior remain unknown. We make only very general assumptions about self-replicating cells: they must conserve mass, obey kinetic rate laws, and maintain constant density over time. We then formulate the corresponding optimization problem on generalized coordinates in close analogy to fundamental theories in physics, and solve it using the Euler–Lagrange equations, which determine the optimal biomass allocation over time for any given self-replicating cell model in any given dynamical growth medium. Finally, we show that the resulting equations of optimal motion not only predict oscillations, but also the well-known phenomenological growth laws observed in various organisms, and a new type of dynamical growth law that has not yet been tested experimentally.

Integrating spatial imaging and intracellular signaling to model emergent tumor–T cell dynamics with multiscale agent-based models

Bi-rong Wang, Federica Eduati

Eindhoven University of Technology, The Netherlands

The tumor microenvironment (TME) is a complex biological system, whose characterization is essential for advancing anti-cancer therapy. Recent imaging innovations have greatly improved our ability to capture the spatial organization of the TME. However, interpreting these data and understanding their implications for tumor progression and therapy response remain challenging. Computational models complement these advances in imaging by providing a framework to integrate spatial and molecular information with biological knowledge to study emergent behaviors in silico. Computational agent-based models (ABMs) are a powerful approach in which a set of rules is defined for both the behavior of individual agents (e.g., proliferation, death) and their interactions with other agents (e.g., migration, immune cell killing of tumor cells). Importantly, ABMs are inherently spatial, meaning that cells are positioned on a grid where interactions occur based on their relative locations. These models are also stochastic, allowing ABMs to capture the variability characteristic of the TME. Our ABM focuses on interactions between tumor cells and cytotoxic T cells, integrating spatial data on TME architecture with phenotypic response data - including apoptosis markers and expression of immunoinhibitory (PDL1) or immunostimulatory (CXCL9/10) molecules - under therapeutic conditions. This design enables investigation of how spatial tumor composition and molecular features jointly influence progression and treatment outcomes. A key strength of our framework is the integration of intracellular signaling effects, allowing the consequences of targeted therapies on cell behavior and cell–cell interactions to be studied mechanistically. To represent intracellular dynamics, we created a modular framework in which different approaches can be tested to simulate cell-specific, intracellular interactions. We tested for instance dynamic models trained on perturbation response data, including logic-ODE models and machine learning surrogate models. Beyond phenotypic response, our model leverages spatial imaging data for both initialization and parameter inference. Microscopy images of 3D in vitro systems are used to define initial spatial configurations, as our model distinguishes variations in tumor progression based on different initial configurations such as hot and cold tumors. We further employ an autoencoder to map imaging data into a latent space that informs and optimizes ABM parameters, linking image-derived features to model behavior. Additionally, within our ABM pipeline, we implemented different analyses including extraction of spatial features, parameter sensitivity analyses, and simulation of in silico drug perturbations. These analyses enable systematic exploration of individual and combinatorial therapy responses, as well as the influence of spatial organization on therapeutic efficacy. Together, our simulations yield insights into emergent tumor behavior, spatially dependent cell–cell interactions, and the dynamics of therapy response, generating experimentally testable hypotheses. Altogether, our multiscale ABM framework bridges spatial imaging, molecular signaling, and computational modeling. By capturing the interplay between tumor architecture and intracellular processes, it provides a valuable tool for interpreting imaging data, predicting therapeutic outcomes, and guiding the development of more effective combinatorial cancer treatments.

From single cells to tumors: computational modeling and analysis of cell populations

Stefan Engblom

Uppsala University, Sweden

This talk explores stochastic modeling approaches for spatial biological processes, motivated by phenomena such as wound healing, gradient sensing in migrating cells, and organoid formation. These systems pose various competing challenges: including large uncertainties, the need for analytical tractability, and modeling flexibility. We begin with a short overview of our previous work in the reaction-diffusion master equation framework, which is well-suited for highly resolved models of individual cells. We then shift focus to the population level, introducing a computational framework designed to address the scale separation inherent in such systems. As a case study, we examine a model of avascular tumor growth---usually described using fluid dynamics-style PDEs. We propose a discrete stochastic alternative and derive an approximate mean-field PDE, enabling analysis of the model's behavior and the influence of key parameters on system responses.

References:

- Blom E, Engblom S. DLCM: a versatile multi-level solver for heterogeneous multicellular systems. Preprint: https://arxiv.org/abs/2504.20565
- Menz G, Engblom S. Modelling Population-Level Hes1 Dynamics: Insights from a Multi-framework Approach. *Bull Math Biol*. 2025;87(6):74. doi:10.1007/s11538-025-01447-9
- Blom E, Engblom S. Morphological Stability for in silico Models of Avascular Tumors. *Bull Math Biol.* 2024;86(7):75. doi:10.1007/s11538-024-01297-x
- Blom E, Engblom S, G. Menz G: Modeling the hallmarks of avascular tumors. In *Numerical Mathematics and Advanced Applications ENUMATH 2023.* 2025. doi:10.1007/978-3-031-86173-4_15. Preprint: https://arxiv.org/abs/2402.01305
- Engblom S. Stochastic Simulation of Pattern Formation in Growing Tissue: A Multilevel Approach. *Bull Math Biol.* 2019;81(8):3010-3023. doi:10.1007/s11538-018-0454-y
- Engblom S, Wilson DB, Baker RE. Scalable population-level modelling of biological cells incorporating mechanics and kinetics in continuous time. *R Soc Open Sci*. 2018;5(8):180379. doi:10.1098/rsos.180379
- Chevallier A, Engblom S. Pathwise Error Bounds in Multiscale Variable Splitting Methods for Spatial Stochastic Kinetics. *SIAM J. Numer. Anal*. 2018;56(1):469-498. doi:10.1137/16M1083086

Sensitive detection of copy number alterations in low-quality liquid biopsy sequencing data

Lotta Eriksson, Eszter Lakatos

Chalmers University of Technology, Department of Mathematical Sciences, Sweden

Liquid biopsies, coupled with analysis of copy number alterations (CNAs), have emerged as a promising tool for non-invasive monitoring of cancer progression and tumor composition. CNAs, which involve large genomic gains or losses, are prevalent in cancer and can be detected using low-pass liquid biopsy sequencing. This approach offers a cost-effective and minimally invasive alternative to traditional tissue biopsies. However, methods utilizing CNA data from liquid biopsies are limited by the low signal in the samples, caused by a low percentage of cancer DNA in the blood, and the inherent noise introduced during sequencing, which limits the strength of the detectable signal. To address this challenge, we developed BayesCNA, a method designed to improve signal extraction from low-pass liquid biopsy sequencing data, by utilizing a Bayesian changepoint detection algorithm.[1,2] We identify positions in the genome with high posterior changepoint probability to identify the locations of CNAs. We show the effectiveness of the method on synthetically generated datasets, and compare the method to state-of-the-art bioinformatics tools under noisy conditions. Our results show that this novel approach increases sensitivity in detecting CNAs, particularly in low-quality cases.

1. Barry D, Hartigan JA. Product Partition Models for Change Point Problems. *Ann. Statist.* 1992;20(1):260-279. doi:10.1214/aos/1176348521
2. Barry D, Hartigan JA. A Bayesian Analysis for Change Point Problems. *J Am Stat Assoc.* 1993;88(421):309-319. doi:10.1080/01621459.1993.10594323

Mathematical Modeling of Canonical–Noncanonical NF-κB Crosstalk Driving Early CD8^{+} T-Cell Fate Bifurcation and Long-Term Effector–Memory Balance

Rifaldy Fajar[1], Rini Winarti[2], Prihantini Prihantini[1]

[1]AI-BioMedicine Research Group, IMCDS-BioMed Research Foundation, Indonesia; [2]Department of Biology, Yogyakarta State University, Indonesia

Background and Aim: Canonical and noncanonical NF-κB pathways regulate how dendritic cells (DCs) initiate CD8^{+} T-cell activation, but their dynamic interplay and downstream impact on effector–memory balance remain poorly quantified. Canonical RelA/p50 signaling rises rapidly, whereas noncanonical RelB/p52 accumulates more gradually and persistently, suggesting that their relative dominance may shape the early "fate-bifurcation window" in CD8^{+} T-cell priming. Single-cell data indicate that these early hours determine long-term lineage outcomes, and no existing framework links DC NF-κB dynamics to T-cell regulatory-network transitions. Understanding this multi-scale pathway control is essential for improving vaccine durability, infection clearance, and immunotherapy responses. Methods: We constructed a multi-scale mathematical model linking DC NF-κB dynamics to CD8^{+} T-cell fate transitions using transcriptomic and single-cell datasets. At the DC level, a 9-equation ordinary differential equation system captured canonical $\mathrm{IKK}_{\beta}-\mathrm{I\kappa B}_{\alpha}-\mathrm{RelA/p50}$ and noncanonical $\mathrm{NIK}-\mathrm{p100}\rightarrow\mathrm{p52}-\mathrm{RelB/p52}$ signaling modules, derived through systematic model reduction while preserving essential dynamical behavior. Time-resolved nuclear RelA and RelB outputs served as inputs to a stochastic T-cell fate-decision model integrating a six-node transcription factor network (Tcf7, Bcl6, Eomes, Tbx21, Prdm1, Id2) represented through an energy-landscape formulation reconstructed from early single-cell distributions. Bayesian parameter estimation with 20,000 posterior samples ensured stable inference, and global Sobol sensitivity analysis quantified pathway influence on state transitions. External validity was tested through RelA/RelB perturbations of $\pm 20\%$ and simulations of 100,000 virtual T cells across 500 bootstrap replicates. Results: The DC module reproduced canonical RelA/p50 early peaks at 1.9-fold activation (95% CI 1.72–2.03) and noncanonical RelB/p52 accumulation at 2.4-fold (95% CI 2.18–2.61). The integrated model aligned with early CD8^{+} T-cell divergence metrics ($\mathrm{R}^2 = 0.87$, RMSE = 0.09) and matched effector–memory proportions at day 7 (63:37% vs 61:39%). Reducing RelB input by 20% decreased effector commitment by -14.8% (95% CI -12.1 to -17.5) and increased memory-like states by +11.6% (95% CI 9.0–14.2%), whereas enhancing RelB by 20% increased effector differentiation by +18.9% (95% CI 15.5–22.3%) and raised long-term exhaustion probability by +9.7% (95% CI 7.8–11.5%). Sobol analysis identified NIK-dependent $\mathrm{p100}\rightarrow\mathrm{p52}$ processing as the dominant bifurcation-controlling parameter (index 0.41), followed by RelA nuclear retention (0.27). Predictions remained consistent with <4% variability across bootstrap simulations. Timing perturbations of ± 3 hours shifted the early lineage-bias index by up to 12%, with the strongest effects in intermediate precursor populations, consistent with heterogeneity observed in early priming responses. Conclusions: This study provides a quantitative multi-scale reconstruction of how canonical–noncanonical NF-κB crosstalk in DCs governs early CD8^{+} T-cell fate bifurcation and long-term effector–memory balance. Moderate modulation of RelB signaling leads to meaningful shifts in immune potency and exhaustion probability, indicating pathway elements relevant to vaccine adjuvant design, chronic infection management, and immunotherapy durability. The integrated ODE–stochastic framework establishes a rigorous approach for mathematical modeling of cellular signaling-to-fate transitions in immune biology.

Cell Trajectory Inference based on Schrödinger problem and a mechanistic model of stochastic gene expression

Clémence Fournié[1], Fabien Crauste[1], Olivier Gandrillon[2]

[1]Université Paris Cité, CNRS, MAP5, Paris, France; [2]ENS Lyon, LBMC and Inria, France

Cellular differentiation is the biological process that leads a cell to opt for a particular cellular identity. Recently, single-cell RNA-sequencing has enabled the simultaneous measurement of gene expression levels at specific times for a large number of individual cells and a large number of genes. Repeating such measurements at different timepoints gives then access to the temporal variation, or transport, of a distribution on a gene expression space. The temporal trajectory of the distribution characterizes the differentiation process. However, current methods for inferring differentiation trajectories, based on optimal transport theory, assume that cells evolve by diffusion in gene expression space, when real gene dynamics are much more complex. We propose a modified optimal transport method that incorporates a model of gene dynamics, called the Bursty model, which assumes that mRNA dynamics are characterized by brief and important production of RNA, with long periods of inactivity in between. This model has been demonstrated to accurately reproduce realistic mRNA and protein dynamics at the single-cell level. By comparing solutions to the Schrödinger problem (equivalent to the optimal transport problem) under both diffusion and the Bursty model, we demonstrate, using simulated data, that our approach better captures the complexity of cellular trajectories. We apply our approach on single-cell RNA-sequencing data from a neuroblastoma organoid.

Stochasticity contributes to explaining heterogeneity in mitochondrial engagement during apoptosis

Jenny Geiger[1], Fabian Klötzer[1], Nadine Pollak[1,2], Gavin Fullstone[1,2,3#], Markus Rehm[1,2#]

[1]Institute of Cell Biology and Immunology, University of Stuttgart, Stuttgart, Germany; [2]Stuttgart Research Center Systems Biology, University of Stuttgart, Stuttgart, Germany; [3]School of Medicine, Pharmacy and Biomedical Sciences, University of Portsmouth, Portsmouth, United Kingdom

[#]shared last authorship

Apoptosis dysfunction is linked to diseases like cancer and neurodegenerative disorders. A key event during apoptosis is mitochondrial outer membrane permeabilization (MOMP), which typically proceeds in a rapid all-or-none fashion. If MOMP occurs only in a subset of mitochondria (minority MOMP), it can be sublethal and contribute to tumorigenesis and cancer progression. Similarly, individual mitochondria escaping widespread MOMP (majority MOMP) can allow cancer cells to recover if apoptosis execution fails. How such heterogeneities in mitochondrial MOMP responsiveness arise within cells is incompletely understood. In particular, whether stochasticity in subcellular protein distributions and interactions across cytosol and mitochondria can realistically contribute to mitochondrial MOMP heterogeneity has not yet been studied. We developed a particle-based, spatially resolved computational model to investigate whether stochasticity in protein distributions and molecular interactions can realistically account for mitochondrial MOMP heterogeneity. Our modeling approach sequentially integrated cytosolic and mitochondrial compartments at cellular scale, incorporating a reduced interactome of key apoptotic regulators (MCL-1, BAK, tBID). Through high-performance computing, we performed cell-scale simulations to mathematically analyze how stochastic effects in protein distributions influence MOMP susceptibility across mitochondrial populations. Our results revealed that stochasticity strongly predisposes small or fragmented mitochondrial sub-pools to MOMP under low apoptotic stress conditions. At higher apoptotic stress levels, fractions of small mitochondria also were more likely to escape MOMP than large mitochondria. Retrospective quantification of mitochondrial sizes in experimental scenarios of minority and majority MOMP validated these computational predictions, demonstrating strong concordance between model-derived and experimental observations.

From data to dynamics: mechanistic models illuminate the clonal evolution of hematopoietic stem cells

Ingmar Glauche[1], Sebastian Wagner[2], Yuri Garcia Vilela[3], Lars Thielecke[1], Artur César Fassoni[4]

[1]TU Dresden, Dresden, Germany; [2]Gesundheitsforen Leipzig GmbH, Leipzig, Germany; [3]Universidade Federal de Minas Gerais, Belo Horizonte, Brazil; [4]Universidade Federal de Itajubá, Itajubá, Brazil

Hematopoietic stem cells (HSCs) maintain lifelong blood production by balancing self-renewal and differentiation. Clonal dynamics among these cells provide critical insights into both the physiological organization of hematopoiesis and the development of hematological diseases. Advances in sequencing technologies and longitudinal clonal analysis, combined with mechanistic mathematical modeling, now offer unprecedented insights into the dynamic principles underlying HSC organization. We report on two exemplary cases illustrating the power of such integrative approaches. Clinical investigations have revealed that clonal dominance often emerges early in life and expands gradually over decades, presenting significant challenges for detecting and monitoring initially rare clones that may eventually contribute to disease development. We use a modeling framework to investigate the limitations of accurately quantifying the dynamics of small but slowly expanding clones over short observation periods. Our results show that intrinsic stochastic fluctuations dominate early clonal competition, particularly for low-abundance clones (around 1% clonal contribution), leading to an apparent overrepresentation of stable or shrinking clones in short-term analyses. High-resolution clonal tracking also provides a powerful resource to investigate the divisional dynamics of HSCs, particularly the role of quiescence and the intrinsic heterogeneity of the stem cell pool. Here, we apply mechanistic mathematical modeling to longitudinal clonal data from non-human primates. We show that models treating HSCs as a single, homogeneous population can reproduce the gradual loss of clonal diversity but fail to capture clone size distributions and the long-term persistence of small and late-appearing clones. We demonstrate that a stochastic two-compartment model in which HSCs transition reversibly between an actively cycling state and a quiescent, niche-associated state better reproduces the experimental data. Our results demonstrate that mechanistic modeling provides an essential framework for the quantitative interpretation of clonal data in hematology. Such integrative approaches offer a basis for improved diagnosis, risk stratification, and therapeutic intervention in clonal hematopoiesis and related disorders.

Modelling transient behaviour changes during the 2022 mpox outbreak using temporal adaptive networks

Nils Gubela[1], Max von Kleist[1,2]

[1]Freie Universität Berlin, Germany; [2]Robert Koch-Institut, Berlin, Germany

Mpox denotes a viral zoonosis caused by the Orthopoxvirus monkeypox (MPXV), which is endemic in West and Central Africa. In spring 2022, notable outbreaks of MPXV clade IIb were recorded in several high-income countries, predominantly affecting men who have sex with men (MSM). At the peak of the outbreak, over 200 new mpox cases per week were reported in Berlin, which constitutes one of the largest MSM population in Europe. Within the same year, the outbreak significantly declined, and it is unclear which factors contributed to this rapid decrease. To investigate the concomitant effects of sexual contact networks, transient contact reductions and the effect of infection- vs. vaccine-derived immunity on the 2022 mpox outbreak, we developed and calibrated a temporal adaptive network model with epidemic, vaccination, contact- and behavioural data. Until now, simulating systems of this size was unfeasible; however, our introduction of a rejection-based stochastic sampling algorithm enables us to sample spreading processes on adaptive temporal networks significantly faster than Gillespie's algorithm, while maintaining exactness. Our results indicate that vaccination had a marginal effect on the epidemic decline. Rather, a combination of infection-induced immunity of high-contact individuals, as well as transient behaviour changes reduced the number of susceptible individuals below the epidemic threshold. However, the 2022 mpox vaccination campaign, together with infection-derived immunity may contribute to herd-immunity in the Berlin MSM population against ongoing clade I mpox outbreaks, responsible for the death of over 1,800 individuals in Kongo alone. Demographic changes and immune waning may deteriorate this herd immunity over time.

Modeling time-dependent vaccine efficacy and re-vaccination dynamics in an extended SIRS framework

Joseph Páez Chávez[1], Aytül Gökçe[2], Thomas Götz[3], Burcu Gürbüz[4]

[1]Escuela Superior Politecnica del Litoral Ecuador, Guayaquil, Ecuador; [2]Ordu University, Turkey; [3]University of Koblenz, Germany; [4]Johannes Gutenberg-University Mainz, Germany

In this study, we develop an extended SIRS model that integrates waning vaccine efficacy and periodic re-vaccination to study infectious disease dynamics under time-limited immunity. The model combines continuous and discrete formulations to analyze equilibrium behavior, stability, and bifurcation patterns. Our results reveal bistability and backward bifurcations, demonstrating that vaccination alone may not ensure disease eradication when immunity decays. To address this, we formulate an optimal control framework balancing vaccination rate, re-vaccination timing, and non-pharmaceutical interventions (NPIs). Numerical continuation and bifurcation analyses show that coupling vaccination with adaptive contact restrictions significantly reduces infection prevalence and control costs. The study provides a quantitative basis for designing efficient and sustainable immunization strategies in the presence of waning immunity.

Federated Latent Transition Models for Post-Acute Infection Syndromes

Roy Gusinow

University of Bonn, Germany

The HALTA Long COVID project addresses Post-Acute Infectious Syndromes (PAISs), with Post-COVID-19 condition (PCC) as the most prominent example, where symptoms persist for months and arise from multi-systemic dysfunction. We develop a federated learning infrastructure to analyse sensitive medical data that remain stored across hospitals and research centres. This architecture enables multi-cohort modelling without the transfer of individual-level records. Within this framework, we implement an interpretable federated latent transition analysis (LTA) approach for PAIS research. The method extracts disease phenotypes directly from the data and quantifies patient-level transitions across follow-up, removing reliance on predefined clinical categories. Covariates can be incorporated to evaluate how demographic or clinical characteristics modulate transitions and long-term outcomes. We integrate data from major European and German post-COVID cohorts—including ORCHESTRA, EuCARE, BeyondCOVID, and EPILOC—to achieve sufficient sample size for robust modelling. With measurements at infection and at 6, 12, 18, and 24 months, we identify distinct PCC phenotypes and complex transition pathways. The federated LTA approach yields interpretable characterisations of symptom evolution, supports privacy-preserving cross-cohort research, and enables data-driven patient stratification. This framework generalises beyond PCC, offering a scalable methodological template for analysing PAISs and other post-infectious conditions in both pandemic and inter-pandemic contexts.

Simulation-based inference for stochastic nonlinear mixed-effects models with applications in systems biology

Henrik Häggström, Sebastian Persson, Marija Cvijovic, Umberto Picchini

Department of Mathematical Sciences, Chalmers University of Technology and the University of Gothenburg, Sweden

The analysis of data from multiple experiments, such as observations of several individuals, is commonly approached using mixed-effects models, which account for variation between individuals through hierarchical representations. This makes mixed-effects models widely applied in fields such as biology, pharmacokinetics, and sociology. In this work, we propose a novel methodology for scalable Bayesian inference in hierarchical mixed-effects models. Our framework first constructs amortized approximations of the likelihood and the posterior distribution, which are then rapidly refined for each individual dataset, to ultimately approximate the parameters posterior across many individuals. The framework is easily trainable, as it uses mixtures of experts but without neural networks, leading to parsimonious yet expressive surrogate models of the likelihood and the posterior. We demonstrate the effectiveness of our methodology using challenging stochastic models, such as mixed-effects stochastic differential equations emerging in systems biology-driven problems. However, the approach is broadly applicable and can accommodate both stochastic and deterministic models. We show that our approach can seamlessly handle inference for many parameters. Additionally, we applied our method to a real-data case study of mRNA transfection. When compared to exact pseudomarginal Bayesian inference, our approach proved to be both fast and competitive in terms of statistical accuracy.

Flavours of Practical Identifiability: Sensitivities, Confidence, and Confusion

Mio Heinrich, Rafael Arutjunjan, Jens Timmer

CIBSS Centre for Integrative Biological Signalling Studies, University of Freiburg, Germany; Freiburg Center for Data Analysis and Modeling, University of Freiburg, Germany

Identifiability is a crucial property of mathematical models – essential for making accurate predictions, estimating parameters, or uncovering new mechanisms. Structural identifiability, that answers the question if the model structure by itself is sufficient, is well defined and can be analysed quickly with various methods and approaches. In contrast, practical identifiability, that analyses the model in combination with an experimental protocol and data, lacks a concise definition that is widely agreed on. We highlight the differences in definitions and analysis methods for practical identifiability. In particular, we differentiate between classifications based on the sensitivity of model parameters and methods that analyse the confidence intervals of parameters, showing how each captures different flavours of identifiability. Finally, we call for clearer, more consistent terminology in discussions of practical identifiability analysis results, such that the employed method is clear from the terminology.

Statistical Test to compare the Linkage Model and the Admixture Model based on Central Limit Results

Carola Sophia Heinzel

Department for Mathematical Stochastics, University of Freiburg, Germany

In the Admixture Model, the probability that an individual carries a certain allele at a specific marker depends on the allele frequencies in K ancestral populations and the proportion of the individual's genome originating from these populations. The markers are assumed to be independent. The Linkage Model (Falush 2003) is a Hidden Markov Model (HMM) that extends the Admixture Model by incorporating linkage between neighbouring loci. This study investigates the consistency and central limit behaviour of maximum likelihood estimators (MLEs) for individual ancestry in the Linkage Model, complementing earlier results by Pfaff (2004), Pfaffelhuber and Rohde (2022), Heinzel (2025) for the Admixture Model. These theoretical results are used to prove theoretical properties of a statistical test that allows for model selection between the Admixture Model and the Linkage Model. Finally, we demonstrate the practical relevance of our results by applying the test to real-world data from the 1000 genomes project. A preprint is available on https://arxiv.org/abs/2509.12734.

A Manually-Curated Stoichiometric Core Model Of Liver Metabolism

Rune Höper, Ralf Steuer

University of Leipzig, Germany

Introduction: Stoichiometric metabolic reconstructions provide an excellent framework to study cellular metabolism in a quantitative way. However, constraint-based analyses are usually based on comprehensive genome-scale reconstructions, which can be difficult to interpret due to their large size, complexity, and possible reconstruction errors, especially for human metabolism. To address this limitation, we are developing HepatoCore, a manually curated, medium-scale stoichiometric model of human liver metabolism designed to balance coverage and interpretability. Methods: HepatoCore is based on existing models and the Metabolic Atlas/Human-GEM to cover essential metabolic functions, including glucose metabolism, lipid metabolism, amino acid synthesis, the urea cycle, and cholesterol biosynthesis, while consisting of fewer than 400 reactions. Careful database annotation allows for direct integration with transcriptomic or other omics datasets. The model is compatible with established stoichiometric analysis methods, including visualization, flux balance analysis, and elementary flux mode analysis. Results and Conclusions: HepatoCore's intermediate size allows simulation of a broad set of hepatic metabolic functions while remaining manageable for detailed analysis and interpretation. The model supports the study of metabolic disorders, such as MASLD and liver cancer, using context-specific flux analysis informed by omics data. Built as a flexible and scalable platform, HepatoCore promotes reproducibility and data-driven studies in systems biology. The model can be used to explore how flux distributions shift from healthy to disease-associated states, including characteristic features of liver cancer such as enhanced glycolysis and altered lipid synthesis.

NoLimits.jl: A flexible Julia framework for nonlinear and latent-state mixed-effects modeling

Manuel Huth, Jonas Arruda, Clemens Peiter, Nina Schmid, Jan Hasenauer

Life and Medical Sciences (LIMES) Institute, University of Bonn, Germany; Bonn Center for Mathematical Life Sciences, University of Bonn, Germany

Nonlinear mixed-effects models are central to longitudinal data analysis across the life sciences, enabling the separation of population-level dynamics from individual variability. Such models underpin applications in pharmacokinetics and pharmacodynamics, disease progression, single-cell dynamics, ecological systems, and growth modeling. However, existing software frameworks often impose restrictive assumptions on model structure, random-effect distributions, observation models, or inference strategies, limiting flexibility when modeling complex biological systems.

Modeling Epithelial-Mesenchymal Plasticity: A Driver of Immune Evasion in Cancer

Paras Jain

Indian Institute of Science, Bangalore, India

The Epithelial-Mesenchymal Transition (EMT) and its reverse, MET, are fundamental processes that drive cancer metastasis and foster phenotypic heterogeneity. Emerging clinical and experimental evidence strongly links cancer cells residing in plastic, mesenchymal, or hybrid Epithelial/Mesenchymal (E/M) states to an immunosuppressive tumor microenvironment (TME) and resistance to immunotherapies. Consequently, understanding the cellular processes governing E-M plasticity is essential for mapping the dynamic acquisition of immune evasion traits. Using computational and mathematical modeling, we have developed a framework for quantifying this E-M plasticity. Specifically, we employ dynamical systems theory to describe two key mechanisms: (1) how stochastic fluctuations in core EMT transcription factors (EMT-TFs) drive spontaneous phenotypic switching, and (2) how epigenetic memory stabilizes the system, leading to stable, potentially irreversible mesenchymal states following long-term induction. From an immunological perspective, these modelled mesenchymal phenotypes are known to actively promote immune evasion by inducing the expression of immunosuppressive checkpoints (e.g., PD-L1), recruiting inhibitory cells (Tregs, MDSCs), and causing the functional exclusion of effector T cells. This talk will bridge these computational findings with their immunological consequences. We assert that the dynamic stability and reversibility of E/M states, rigorously quantified by our mathematical models, can serve as a predictive biomarker for immune evasion potential. Ultimately, targeting the non-genetic heterogeneity dictated by EMT plasticity offers a novel strategy to overcome resistance to current cancer immunotherapies.

Dynamical modeling-informed interpretation of Ki67 positivity

Adrien Jolly, Michael Rieger, Florian Büttner

Department of Medicine 2, Hematology/Oncology, Goethe University Frankfurt, Frankfurt am Main am Main, Germany

Ki67 is a protein with multiple functions during the cell cycle, but it is mostly known as a proliferation marker. Both in cell imaging and flow cytometry, it is usually used as a binary proliferation versus quiescence marker, where a fixed level of fluorescence intensity separates cycling and quiescent cells. It is now established that the protein is degraded continuously in both G1 and G0 phases of the cell cycle and produced in S and G2M.However, the consequences of this expression pattern for the interpretation of binary (Ki67 positive or negative fractions) remain largely unaccounted for, leading to systematic errors, with potentially massive over or underestimation of the quiescent fraction depending on the length of the G1 phase and the degradation kinetics of Ki67. In this work, we describe quantitatively how the percentage of Ki67 positive cells at steady state varies depending on the cell cycle dynamics. For this purpose, we use a realistic population-level mathematical model of the cell cycle that we combine with a literature-informed model of Ki67 kinetics. Briefly, we assume that Ki67 negative cells become positive upon entering the S phase, and that Ki67 fluorescence decays continuously in G0/G1 from a uniform starting level after mitosis. Cells are expected to become Ki67 negative following a semi-deterministic delay and consequently, we model the time for cells to turn negative in G0/G1 with a gamma distribution. With our model, we find that the most significant source of error under typical cell cycle parameters is the misclassification of G0 cells as G1. We further explore various scenarios to determine how Ki67 positivity and S/G2M cells fractions are expected to change upon perturbations and identify characteristic patterns reflecting changes in single cell-cycle phases. Our work provides guidelines for both experimentalists and clinicians to interpret changes in Ki67 positivity.

Molecular signatures of post-acute sequelae of COVID-19

Franziska Kimmig[1], Neha Mishra[1], Matthieu Bourgery[1,2], Anne-Kathrin Ruß[3], Joana Pimenta Bernardes[1], Lennart Reinke[2], Sabrina Ballhausen-Lübcker[2], Jeanette Franzenburg[1], Sonja Kunze[4], Bettina Lorenz-Depiereux[5], Melanie Waldenberger[5,6], Gabriele Anton[7], Florian Tran[1,2], Thomas Bahmer[2,8], Stefan Schreiber[2], Jan Heyckendorf[2], Philip Rosenstiel[1], NAPKON Study Group

[1]Institute of Clinical Molecular Biology, Christian-Albrechts-University and University Hospital Schleswig-Holstein, Campus Kiel, Kiel, Germany; [2]Department of Internal Medicine I, University Hospital Schleswig-Holstein, Campus Kiel, Kiel, Germany; [3]Institute of Medical Informatics and Statistics, Kiel University, University Medical Center Schleswig-Holstein Campus Kiel, Kiel, Germany; [4]Institute of Epidemiology, Helmholtz Center Munich, Munich, Germany; [5]Institute of Epidemiology, Research Unit of Molecular Epidemiology, Helmholtz Munich - German Research Center for Environmental Health, Neuherberg, Germany; [6]German Center for Cardiovascular Disease Research (DZHK), Munich Heart Alliance, Munich, Germany; [7]Medical School OWL, Bielefeld University, Bielefeld, Germany; [8]Airway Research Center North (ARCN), German Center for Lung Research (DZL), Großhansdorf, Germany

The COVID pandemic has profoundly impacted public life and is still affecting the lives of many thousands of people who suffer from post-acute sequelae of COVID-19 (PASC). PASC severity and symptom profiles differ greatly between affected individuals and are influenced by numerous individual factors including sex, vaccination status, infection severity and comorbidities. However, the molecular mechanisms underlying this highly heterogeneous disease and their association with different patient characteristics are still poorly understood. We performed bulk-RNA sequencing and methylation profiling on blood samples of a densely phenotyped cross-sectional cohort of 710 individuals with PCR confirmed cases of SARS-CoV-2 infection 6 to 12 months after the initial infection. PASC severity was measured using a post-COVID syndrome (PCS) score based on 12 non-overlapping long-term symptom complexes of COVID-19.[1] We assessed differences in transcriptomic and epigenetic signatures between disease severities and performed weighted gene co-expression network analysis to identify molecular pathways underlying different symptom complexes, their association with patient characteristics and their epigenetic regulation. To investigate sex-specific differences in symptom-associated expression and gene regulation we conducted a gene module preservation analysis. Severe PASC as compared to mild PASC was associated with an inflammatory transcriptional profile, mitochondrial dysfunction, and downregulation of adaptive immune system processes. Methylation profiles presented with overall hypomethylation of sites in high disease severity. Co-expression analysis yielded several symptom-related gene sets including one module comprising genes involved in defense response to virus which was correlated with pulmonary ailments. Furthermore, we identified one gene cluster associated with exercise intolerance that was related to Il1-beta production, pre-existing pulmonary and neurological ailments, and increased CRP. Sex-stratified analysis revealed multiple sex-specific gene networks related to fatigue, neurological symptoms, and sleep disturbance. Interestingly, most symptom associations were present only in male participants with for example one eosinophil related gene set showing a male-specific association with neurological ailments and fatigue. Our results suggest immune dysregulation and a complex interplay of clinical factors underlying PASC severity and symptoms occurrence. Predominance of male-specific associations of molecular signatures with symptoms indicate high heterogeneity in female participants, potentially due to patient subsets with differing immune profiles. While further analysis is required to test for these patient subgroups, our findings provide pathway-symptom relations and their connection to patient profiles that can be targeted in future research.

1. Bahmer T, Borzikowsky C, Lieb W, et al. Severity, predictors and clinical correlates of Post-COVID syndrome (PCS) in Germany: A prospective, multi-centre, population-based cohort study. *EClinicalMedicine*. 2022;51:101549. doi:10.1016/j.eclinm.2022.101549

Quantitative analysis of CODEX multiplexed histological imaging data in the tumour microenvironment

Lukas Kiwitz[1], Roberta Turiello[1], Maike Effern[1], Susanna Ng[1], Sonia Leonardelli[1], Sarah Eickhoff[1], Marieta Toma[2], Jennifer Landsberg[3], Michael Hölzel[1], Kevin Thurley[1]

[1]Biomathematics Division, Institute of Experimental Oncology, University Hospital Bonn, Bonn, Germany; [2]Institute of Pathology, University Hospital Bonn, Bonn, Germany; [3]Department of Dermatology and Allergy, University Hospital Bonn, Bonn, Germany

The tumour microenvironment (TME) is a complex biological niche populated by tumour cells, stromal cells and immune cells. A better quantitative understanding and characterization of this environment and its heterogeneity between patients is of vital importance in developing effective treatment strategies. In particular, the presence of different immune cell populations within the TME play a major role in cancer progression, yet the spatial composition of specific immune sub-populations in the TME is only beginning to emerge and quantitative analysis is largely lacking. Here, we describe a quantitative, modular open-source framework for processing multiplexed fluorescence-histology data from the CODEX platform, single cell and spatial analysis as well as predictive modeling of clinical outcomes. CODEX allows for the simultaneous measurement of more than 40 fluorescent markers on a single tissue section (FFPE, formalin-fixed paraffin embedded) by fully automated staining and imaging cycles. Our framework addresses several challenges in currently available data analysis protocols incl. treatment of structured noise and antibody variability leading to more robust single cell features, accurate single cell annotation and the creation of biologically informed spatial readouts. We will leverage this spatial information to quantitatively characterize the spatial tissue architecture on large clinical cohorts and design data-driven spatio-temporal models of immune cell dynamics in the TME.

Rare functional variants in FBN2 are strong genetic determinants for bicuspid aortic valve disease

Laura Koebbe

Institute for Human Genetics, University Hospital Bonn, Germany

Bicuspid aortic valve (BAV) is the most common congenital heart defect, defined by the presence of two instead of three valve leaflets. BAV is of great clinical relevance since it is a major precursor to serious cardiovascular complications. Given that the genetic basis of BAV remains incompletely understood, we aimed to identify novel risk genes and elucidate the underlying molecular mechanisms. We conducted the largest whole-exome sequencing (WES) study of BAV to date, including 1,030 European cases. Gene-based burden analysis identified FBN2 as novel and major genetic determinant, accounting for 3.2% of all cases. This represents a higher burden for BAV than the combined contribution of all previously established monogenic BAV genes. Beyond BAV, carriers of FBN2 rare variants (RVs) frequently exhibited brachydactyly, suggesting a syndromic presentation involving cardiovascular and skeletal phenotypes. Genetic validation using WES data from > 370,000 UK Biobank (UKB) participants revealed an increased prevalence of aortic valve stenosis, of which BAV is the most common cause, among FBN2 RV carriers. Functional assays in patient-derived fibroblasts demonstrated that the RVs lead to FBN2 deficiency, promoting aberrant extracellular matrix remodeling and impairing the sequestration of transforming growth factor-β (TGF-β) and bone morphogenetic protein (BMP). Dysregulated TGF-β signaling during embryonic development appears to perturb the tightly regulated spatiotemporal patterning required for proper separation of the three aortic valve leaflets, resulting in BAV formation. While increased TGF-β activity typically promotes skeletal overgrowth and arachnodactyly, the brachydactyly observed in FBN2 RV carriers likely results from simultaneously enhanced BMP signaling that counterbalances TGF-β effects. In vivo, fbn2b-deficient zebrafish show severe outflow tract valve malformations, confirming an essential role for fibrillin-2 in cardiac valve development. In conclusion, FBN2 represents a novel and major genetic determinant of BAV. FBN2-related BAV defines a new fibrillinopathy characterized by combined cardiovascular and skeletal manifestations and should be particularly suspected in patients presenting with both BAV and brachydactyly. Future work will focus on integrating multi-omics data into a comprehensive human interactome, enabling the modeling of gene-gene and pathway-level perturbations. Network propagation and expansion algorithms will uncover additional risk genes and associated cellular processes underlying BAV.

HallmarkGraph: a cancer hallmark informed graph neural network for classifying hierarchical tumor subtypes

Qingsong Zhang[1], Fei Liu[1], Xin Lai[2,3]

[1]South China University of Technology, Guangzhou, China; [2]Tampere University, Finland; [3]University Hospital of Erlangen, Germany

Accurate tumor subtype diagnosis is crucial for precision oncology, yet current methodologies face significant challenges. These include balancing model accuracy with interpretability and the high costs of generating multi-omics data in clinical settings. Moreover, there is a lack of validated models capable of classifying hierarchical tumor subtypes across a comprehensive pan-cancer cohort. We present a graph neural network, HallmarkGraph, the first biologically informed model developed to classify hierarchical tumor subtypes in human cancer. Inspired by cancer hallmarks, the model's architecture integrates transcriptome profiles and gene regulatory interactions to perform multi-label classification. We evaluate the model on a comprehensive pan-cancer cohort comprising 11,476 samples from 26 primary cancers with 405 subtypes up to eight levels. The model demonstrates exceptional performance, achieving 5-fold cross-validation accuracy between 85% and 99% for tumor subtypes labeled with increasing details of genomic information. It also shows good generalizability on a validation dataset of 887 samples, assessed using three metrics that consider tumor subtypes at individual, combined, and sample levels. Benchmarking and ablation experiments show that hallmark-based embeddings slightly influence model performance, while the integrated multilayer perceptron plays a significant role in determining classifier accuracy. Additionally, we use the SHAP method to link cancer hallmarks with genes, identifying key features that influence model decisions. Our findings present a biologically informed machine learning framework capable of tracking tumor transcriptomic trajectories and distinguishing inter- and intra-tumor heterogeneity in pan-cancer. This approach holds promise for enhancing cancer diagnostics.

Impact of the COVID-19 pandemic on the acquisition of ESBL-producing *Klebsiella pneumoniae* in hospitals: a modelling study on the intensive care unit of Guadeloupe

Maylis Layan[1,2,3,4], Eva Mellan[5], Benoît Tressières[5], Marc Valette[6], Sébastien Breurec[5,7,8,9], Laura Temime[3,4#], Lulla Opatowski[1,2#]

[1]Epidemiology and Modelling of Antibiotic Evasion unit (EMAE), Institut Pasteur, Université de Paris, Paris, France; [2]CESP, Anti-infective evasion and pharmacoepidemiology team, Université Paris-Saclay, UVSQ, Inserm, Montigny-Le-Bretonneux, France; [3]Modélisation, épidémiologie et surveillance des risques sanitaires (MESuRS), Conservatoire national des arts et métiers, Paris, France; [4]PACRI unit, Institut Pasteur, Conservatoire national des arts et métiers, Paris, France; [5]Clinical Investigation Center Antilles-Guyane, Unit 1424, Inserm, Pointe-à-Pitre, Guadeloupe, France; [6]Intensive Care Unit, University Hospital of Guadeloupe, Pointe-à-Pitre, Guadeloupe, France; [7]Clinical Microbiology Group, Institut Pasteur of Guadeloupe, Les Abymes, France; [8]Clinical Microbiology Laboratory, University Hospital of Guadeloupe, Pointe-à-Pitre, Guadeloupe, France; [9]Pathogenesis and Control of Chronic and Emerging Infections, University of Montpellier, Inserm, Établissement français du sang, University of Antilles, Pointe-à-Pitre, France

[#]shared last authorship

The COVID-19 pandemic has led to major disruptions in hospitals affecting patient casemix, care organization, antimicrobial stewardship programs, and infection prevention and control practices. While some of these factors may have promoted antibiotic resistance, others may have limited its spread. Here, we aimed to disentangle the impact of the COVID-19 pandemic on antibiotic resistance in hospitals by conducting a retrospective study between 2020 and 2022 in the intensive care unit (ICU) of the University Hospital of Guadeloupe, a French overseas territory in the Caribbean. Using microbiological test results of all hospitalized patients over four periods — before SARS-CoV-2 introduction in Guadeloupe, during the Alpha wave, during the Delta wave, and during a SARS-CoV2 endemic period — we identified and evaluated individual and organisational risk factors of ESBL-producing *Klebsiella pneumoniae* (ESBL-KP) acquisition. We analysed the collected data using stochastic individual-based models of ESBL-KP acquisition accounting for the inclusion period or individual risk factors (third-generation cephalosporins use, SARS-CoV-2 positivity, mechanical ventilation), and information on healthcare workers. We fitted models to the individual-level data from the 4 periods in a Bayesian framework with data augmentation to handle missing microbiological test results. Using the Deviance Information Criterion (DIC) for model comparison, we found that the best model included mechanical ventilation as the only risk factor with a daily ESBL-KP acquisition rate of 0.046 (95% CrI: 0.030-0.064) in ventilated patients compared with 0.012 (95% CrI: 0.00050-0.059) in non-ventilated patients, irrespective of the pandemic period. This difference in acquisition rates had a strong posterior support (Bayes factor=13.0). Interestingly, information on healthcare workers did not improve the fit (ΔDIC < 5). Although about half of the patients were not tested, our results were little affected when excluding untested patients. Overall, our results highlight how the COVID-19 pandemic may have indirectly changed ESBL-KP epidemiology due to more frequent invasive medical procedures, including ventilation. This demonstrates the importance of long-term antibiotic resistance surveillance in hospitals, with sustained efforts during pandemic times.

Physical-Chemistry of Cell Physiology: a top-down, transdisciplinary approach from obvious biological statements to interwoven multiscale algebraic dynamical systems and the need for a tractable mathematical framework

Jeanne Le Clézio

LP2M, INPHYNI, CNRS, Université Côte d'Azur, France

Living cells are complex entities characterised by continuous exchanges of chemical material and energy between micrometric compartments separated by a nanometric membrane. In this presentation, we examine how theses exchanges take place across the membrane to ensure the homeostasis (a.k.a the steady state) of a cellular system, with a view to understand its response to a perturbation: this is a key question at the interface between mathematics, physics, chemistry, and biology. The cell membrane carries different types of matter transporters, and acts as a first dynamical system. As the membrane separates charges, it also acts as a capacitor and ends up with a local electric potential. We will detail the different kinds of transports, namely the enzymatic exchangers, the electro-osmotic passive channels, and how derive their fluxes through the polarized membrane. Because the transported matter is involved into chemical reactions, each side of the membrane is a local chemical reactor. Given the knowledge of all the possible reactions and their kinetic rates, we could describe the chemical part as another dynamical system. Unfortunately, very little data is available compared to the numerous possible reactions. Nonetheless, while comparing the characteristic relaxation times of the chemical components to the membrane transport rates, we concluded that it was possible to assume that the chemical reactions are fast and that we may consider that they form a steady-state sub-system which instantaneously adapts to the locally injected or expelled matter. Hence we will show how to solve the chemical problem with the simple assumption that the reactive species obey a set of known equilibria. We will also point out a few drawbacks arising from the algebraic coupling between the equilibria and the subsequent numerical problems due to the large fluctuations of concentrations. So far, our approach was designed for homogeneous media (interior and exterior of the cell), but diffusion and migration of species represent as well a key factor in biology (i.e neurotransmission, interstitial drainage...) and consequently modulate the cell behavior. The highly ionic nature of the involved components triggers the need for electophoretic coupling: we will investigate how the tight coupling between ions (in space and time) impacts the physiological transport and present a set of novel reaction-diffusion-migration equations. The purpose of this presentation it to emphasize the underlying mathematics concepts and methods that are mandatory to achieve a biological, physical and chemical cell model with a quantitative description. This work aims to develop a fully tractable 3D model that can reproduce cellular ion transport independently of experimental data. The model should be adaptable to different cell types via the choice of initial conditions and capable of simulating perturbations.

The role of metabolism in shaping enzyme structures over 400 million years of evolution

Oliver Lemke[1,2]*, Benjamin Murray Heineike[3]*, Markus Ralser[1,2,3,4]

[1]Department of Biochemistry, Charité - Universitätsmedizin Berlin, Berlin, Germany; [2]Exploratory Diagnostic Sciences, Berlin Institute of Health at Charité, Berlin, Germany; [3]Center for Human Genetics, Nuffield Department of Medicine, University of Oxford, Oxford, UK; [4]Max Planck Institute for Molecular Genetics, Berlin, Germany

*shared first authorship

Due to a lack in available protein structures, it was challenging to link structural and metabolic evolution in the past decades. With recent developments in structural predictions, especially with the release of AlphaFold 2, closing this gap became achievable by enabling analysis on an atomistic scale. In our effort to understand metabolic evolution on a structural level, we predicted and analyzed over 10,000 enzyme structures from 26 yeasts of the Saccharomycotina subphylum covering 361 metabolic reactions in 225 pathways spanning 400 million years of evolution. We backed up the data by curated databases, mass-spectrometry-based proteomics, flux simulations, experimentally determined structures and an evolutionary analysis. Performing analyses from species metabolic specialization down to the atomistic structural level, we investigated how metabolism affected the structural evolution on different scales. We show how enzymes evolved differently based on their molecular function, highlight metabolic-cost- and enzyme-abundance-dependent effects and examine signatures of positive selection. We report a hierarchical pattern of structural evolution enabling the identification of regions with high structural conservation. Altogether, these findings will contribute to increase the understanding of the relationship between structural and metabolic properties and can be utilized for enzyme annotation, metabolic network engineering or biotechnological applications. Our work was recently published in Nature: https://www.nature.com/articles/s41586-025-09205-6.

Towards data-based mathematical models of spatiotemporal immune-cell interactions

Lisa Li[1], Robin Müller[1], Lorena Pohl[2], Jonas Wehrenberg[3], Andreas Hutloff[3], Barbara Niethammer[2], Kevin Thurley[1]

[1]University Hospital Bonn, Germany; [2]Institute for Applied Mathematics, University of Bonn, Germany; [3]Institute of Immunology, UKSH Kiel, Germany

In secondary lymphoid organs, activated T helper cells differentiate into effector cells and secrete cytokines that orchestrate the activation and differentiation of surrounding immune cells. Previous studies have shown significant spatial inhomogeneities in cytokine distribution, which strongly affect paracrine signaling.[1-3] However, the mechanisms governing the emergence and regulation of these cytokine gradients remain poorly understood. We developed a 3D modeling framework to systematically investigate the formation and influence of spatially varying cytokine concentrations in lymph nodes.[3] Our findings confirmed the necessity of cytokine inhomogeneities for efficient paracrine signaling, and that receptor feedback and tissue architecture further modulate this process. Based on that work, we applied a receptor mean-field approach to develop a more efficient model of cytokine dynamics. Using a homogenization technique, we derived correction terms that enhance the accuracy of these mean field equations, particularly in high cell density environments. The increased model efficiency enabled large-scale simulations to examine the effect of cell motility on cytokine signaling. Using this framework, we are currently investigating the early development of T follicular helper cells in lymph nodes, incorporating timecourse histology data from transgenic reporter mouse strains. Overall, our simulations highlight the complex spatio-temporal dynamics of cell-cell signaling mediated by diffusible ligands, emphasizing the critical role of fine-tuned biological regulation in these processes.

1. Altan-Bonnet G, Mukherjee R. Cytokine-mediated communication: a quantitative appraisal of immune complexity. *Nat Rev Immunol*. 2019;19(4):205-217. doi:10.1038/s41577-019-0131-x
2. Thurley K, Gerecht D, Friedmann E, Höfer T. Three-Dimensional Gradients of Cytokine Signaling between T Cells. *PLoS Comput Biol*. 2015;11(4):e1004206. doi:10.1371/journal.pcbi.1004206
3. Brunner P, Kiwitz L, Li L, Thurley K. Diffusion-limited cytokine signaling in T cell populations. *iScience*. 2024;27(6):110134. doi:10.1016/j.isci.2024.110134

Parametric and Functional Identifiability for Universal Differential Equations

Torkel Loman, Ruth Baker

University of Oxford, UK

Mathematical modelling has traditionally relied on detailed system knowledge to build mechanistic models. However, the rise of methods for large-scale data collection methodologies, together with advances in machine learning, has led to an increasing use of data-driven approaches. Recently, hybrid modelling paradigms have emerged that combine both approaches: well-understood system components are modelled mechanistically, while unknown parts are inferred from data. Here, we focus on one such class: universal differential equations (UDEs), where neural networks are embedded within differential equations to approximate unknown dynamics. When fitted to data, these neural networks act as universal function approximators, learning unknown functional system components. This could be used to e.g. learn a protein's rate of production (as a function of a transcription factor's concentration), or the rate of infection in an epidemic (as a function of the number of infected individuals). In this work, we study identifiability, i.e. our ability to recover true system properties, for UDEs. This is a key challenge, as the neural networks' flexibility greatly increases model degrees of freedom, something which is known to promote identifiability issues. We show that UDE identifiability can be decomposed into parametric and functional components, corresponding to the mechanistic and data-driven model parts, respectively. We will first, briefly, demonstrate how structural functional identifiability can be assessed, before considering practical identifiability. Here, we show how parametric identifiability can be assessed using contemporary tools such as profile likelihood analysis, and how functional identifiability can be evaluated through ensemble plots of fitted functions. Using these techniques, we explore how UDE identifiability depends on model structure, including the simultaneous fitting of multiple neural network functions and the introduction of constraints such as monotonicity. Across a range of examples, from systems biology and population dynamics to epidemiology, we find that generalising a fully mechanistic model to a UDE often has a surprisingly minor impact on identifiability. This suggests that UDEs offer a practically tractable and interpretable framework for handling unknown dynamics in real-world biological systems.

Regulation of ultradian pulsatility and stress responses in the human HPA axis

Belinda Lombard[1], Thomas Upton[2], Ben Gibbison[3], John Terry[4], Stafford Lightman[2], Eder Zavala[5,6,7]

[1]University of Birmingham, Birmingham, UK; [2]Henry Wellcome Laboratories for Integrative Neuroscience and Endocrinology, Translational Health Sciences, Faculty of Health Sciences, University of Bristol, Bristol, UK; [3]Department of Anaesthesia, Bristol Medical School, University of Bristol, Bristol, UK; [4]Neuronostics Ltd, Bristol, UK; [5]Centre for Biological Timing, University of Manchester, Manchester, UK; [6]Division of Diabetes, Endocrinology and Gastroenterology, University of Manchester, Manchester, UK; [7]Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK

The hypothalamic-pituitary-adrenal (HPA) axis is the endocrine system controlling dynamic responses to stressors. Mathematical modelling and experiments in rodents have shown that negative feedback loops underpin rhythmic activity within this axis, but a human equivalent model is lacking. This talk outlines a data-driven approach to calibrate a model of hormonal rhythms in the human HPA axis. The model is written in terms of Delay Differential Equations (DDEs) and predicts the conditions that lead to pulsatile secretion of cortisol and ACTH hormones with ultradian (<24 hrs) periodicity. Oscillatory solutions arise via a Hopf bifurcation, physiologically determined by a balance between the hypothalamic circadian drive and feedback loop delay. The model was calibrated using data consisting of cortisol and ACTH plasma hormone profiles measured every 20 minutes over 24 hrs in 10 healthy individuals. Wavelet analysis revealed unique patterns in hormonal rhythms across individuals, including variability quantification. Model fitting yielded specific parameter values for each participant and estimated cohort distributions. Bifurcation analysis determined the conditions needed to sustain ultradian rhythmicity, and the sensitivity of the oscillatory solution to parameter variability. Coupling a model of sleep regulation will help explore the interactions between stressors and sleep disruptions, offering insights into how circadian rhythms affect neuroendocrine regulation in humans.

Modulatory Principles of Cellular Interactions in Hierarchical Cell Organization

Madhuri Majumder[1,2]*, Hilly Goldner[3,4]*, Shira Yonassi[1,2], Einat Shaer Tamar[1,2], Leeat Keren[5#], Miri Adler[1,2#]

[1]Department of Genetics, Silberman Institute of Life Sciences, Hebrew University of Jerusalem, Jerusalem, Israel; [2]Department of Immunology and Cancer Research, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel; [3]Translational Cancer Research Unit, Sheba Medical Center, Tel-Hashomer, Israel; [4]Computational pathology lab, Sheba Medical Center, Tel-Hashomer, Israel; [5]Department of Molecular Cell Biology, Weizmann Institute of Science, Rehovot, Israel

*shared first authorship; #shared last authorship

Inter-patient variability in cancer treatment response remains a central challenge in oncology. Even among patients with the same cancer type and stage, therapeutic outcomes differ significantly. One of the main factors driving this heterogeneity is the tumor microenvironment (TME)-a complex, dynamic ecosystem composed of stromal and immune cells that interact with malignant cells through growth factors and cytokines. These interactions not only sustain tumor progression but also shape immune composition and influence therapeutic resistance. Despite extensive profiling of the TME, the underlying principles that govern how cell-cell interactions generate compositional variability across patients remain poorly understood. In collaboration with Dr. Leeat Keren (Weizmann Institute of Science), we analyzed multiplex imaging data from pancreatic ductal adenocarcinoma (PDAC) and discovered a striking hierarchical pattern in stromal and immune cell abundance. Fibroblasts were universally present, macrophages appeared with them in most tumors, and T and B cells were found in progressively fewer cases. Notably, certain combinations-such as T and B cells without macrophages-were never observed, suggesting that specific cell-cell communication rules constrain tissue composition results in hierarchical organization. These findings imply that the TME follows an intrinsic organizational logic driven by intercellular signaling networks. To uncover the principles underlying this hierarchy, we developed a mathematical modeling framework that explores all possible interaction circuits among four major cell types: fibroblasts, macrophages, T cells, and B cells. The model integrates nonlinear dynamical systems, graph theory, and combinatorics to identify critical feedback motifs that sustain stable cellular hierarchy. By simulating 4,096 biologically relevant interaction topologies among 65,536, we can determine which growth factor-mediated feedback permit compositional stability and which interactions destabilize the system. Using nullcline and phase-portrait analysis, we identify steady-state structures and reveal how multistability-where multiple stable configurations coexist-can explain observed patient-to-patient variability. Perturbation analysis of these circuits allows us to examine how changes in growth factor production, proliferation, or death rates reshape the TME composition. Sensitivity analysis identifies key parameters and cell types that exert disproportionate influence on hierarchical structure. Integrating model predictions with PDAC single-cell RNA sequencing and spatial tissue data enables detection of ligand-receptor pairs that derived specific interaction patterns leading to hierarchy. Our results suggest that feedback from T cells-B cells circuit to fibroblasts-macrophages circuit is essential for maintaining hierarchical composition, with the T cell-to-fibroblast feedback emerging as the least critical signal, consistent with the observed data. By combining mathematical modeling with experimental validation, this research defined the core modulatory principles that govern hierarchical tissue organization within the TME. Understanding how cellular interactions create and stabilize compositional hierarchy sheds light on the mechanisms underlying inter-patient variability and therapeutic resistance. Ultimately, these insights may guide strategies to re-engineer the tumor microenvironment-enhancing immune infiltration, reducing pro-tumor signaling, and improving treatment efficacy across cancer types.

WAVDeSc: A Wavelet Based Denoising Pipeline for single-cell RNA Sequencing Data Analysis

Isabel Mensah[1], Justice Kwame Appati[2], Sampson Salifu Pandam[3], Peter Amoako-Yirenkyi[1]

[1]Department of Mathematics, KNUST, PMB, Kumasi, Ghana; [2]Department of Computer Science, University of Ghana Legon, PMB, Accra, Ghana; [3]Department of Biochemistry, KNUST, PMB, Kumasi, Ghana

Single-cell RNA sequencing (scRNA-seq) has revolutionized molecular biology for its ability to investigate cell states and functions at unprecedented resolution. Despite its transformative impact in fields of study such as neurobiology, immunology, and developmental biology, scRNA-seq data present inherent challenges, including high noise levels and sparsity, which hinder accurate downstream analysis. In this study, we present WAVDeSc (Wavelet Denoising for Single-cell RNA-seq), a novel gene-wise denoising pipeline that effectively addresses these challenges while preserving essential biological signals. WAVDeSc leverages discrete wavelet transforms to decompose gene expression signals into different frequency components, followed by adaptive level-dependent Bayesian thresholding that removes noise in each component separately. This gene-wise strategy enables targeted noise removal while preserving critical biological variability - a balance that existing methods struggle to achieve. We benchmarked WAVDeSc against four leading denoising methods (MAGIC, SAVER, ENHANCE, DCA) using simulated datasets and real-world data, including human PBMCs and autism spectrum disorder (ASD) brain tissue. WAVDeSc consistently outperformed other denoising methods across key metrics: it achieved superior marker gene preservation, better clustering performance, and higher DEG identification accuracy (F1-score of 0.88, higher than the methods). Critically, in the ASD dataset, WAVDeSc uniquely identified DEGs enriched in neurologically specific pathways (neurogenesis, axonogenesis, synaptic organization), while other methods showed broader, less biologically meaningful enrichment patterns. WAVDeSc also demonstrated remarkable computational efficiency (0.71s average runtime), making it practical for large-scale scRNA-seq studies. In conclusion, WAVDeSc promises to offer a powerful and efficient solution for denoising scRNA-seq data. Its adaptability, performance, and potential to enhance data quality make it a valuable tool for deciphering cellular heterogeneity and gaining deeper insights into complex biological processes at the single-cell level. However, continuous research and refinement will further strengthen its application in future single-cell transcriptomic research.

Multi-Framework Modelling of Population-Level Cellular Signalling

Gesina Menz, Stefan Engblom

Department of Information Technology, Uppsala University, Sweden

Realistically capturing biological behaviour of cellular signalling at the population level requires a careful balance between deterministic and stochastic modelling frameworks. We focus specifically on the Hes1-Notch gene regulatory network, a key pathway involved in developmental patterning. We examine how different mathematical approaches capture its dynamics. We present a multi-framework approach to this signalling pathway by investigating how deterministic ordinary differential equation (ODE) stochastic reaction-diffusion master equation (RDME) models differently represent and capture cell population dynamics. Specifically, we are interested in how to transition between ODE and RDME descriptions of cellular interactions, with particular focus on how the nonlinear behaviours observed in ODE models relate to their stochastic counterparts. Particular emphasis is placed on the transition from sustained oscillations to stable expression states, signalling fate decisions of cells during this developmental process, as an intrinsic property of the pathway. We show this behaviour exhibits high levels of stability under varying levels of noisy conditions in the stochastic setting. Overall, we explore the trade-offs between analytical tractability, biological fidelity and stability to intrinsic noise in this fundamental developmental signalling pathway, aiming to inform the selection and integration of modelling frameworks that best capture the multi-scale and stochastic nature of inter-cellular signalling.

Node persistence from topological data analysis reveals changes in brain functional connectivity

Madhumita Mondal[1,2], Yasharth Yadav[3], Jürgen Jost[4,5,6,7#], Areejit Samal[1,2#]

[1]The Institute of Mathematical Sciences (IMSc), Chennai, India; [2]Homi Bhabha National Institute (HBNI), Mumbai, India; [3]School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore; [4]Max Planck Institute for Mathematics in the Sciences, Leipzig, Germany; [5]Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany; [6]Center for Scalable Data Analytics and Artificial Intelligence, Dresden/Leipzig, Leipzig, Germany; [7]Santa Fe Institute for the Sciences of Complexity, Santa Fe, NM, USA

[#]shared last authorship

Large-scale analyses of brain functional connectivity can uncover disruptions in regional activity and connectivity that are commonly associated with neurological disorders or cognitive decline associated with healthy aging. In our study, we employ persistent homology (PH), a prominent tool in topological data analysis (TDA), to investigate changes in resting-state functional connectivity in healthy aging and autism spectrum disorder (ASD). We analyze functional connectivity changes across three distinct scales: (a) global scale (brain-wide changes), (b) mesoscopic scale (resting-state network-level changes), and (c) local scale (region-level changes). At the local scale, we introduce node persistence, a novel and scalable PH-based measure that detects brain regions with significant differences in healthy aging or ASD. Notably, these regions overlap with regions whose non-invasive stimulation improves motor function in the elderly or alleviates ASD symptoms, suggesting the utility of node persistence in identifying clinically relevant brain regions affected by aging and ASD.

Dissecting the efficacy of Multiple Low Dose Efficacy via computational modelling of EGFR-MAPK inhibition

Paolo Odello[1], Bram Thijssen[1], Kathy Jastrzebski[1], João Neto[1], Lianne Bouwmeester[1], Evert Bosdriesz[2], Lodewyk Wessels[1]

[1]Netherlands Cancer Institute (NKI), Amsterdam, The Netherlands; [2]Vrije Universiteit Amsterdam, The Netherlands

Understanding the molecular mechanisms of cell signaling is of particular interest in the context of targeted anti-cancer therapies, where specific components of the signaling machinery are inhibited in order to block the sustained proliferation of cancer cells. Currently, targeted therapies are the standard of care in several cancers where driver mutations are known to lead to hyperactive signaling pathways. However, despite the initial effectiveness of targeted inhibitors, the cancers often develop resistance to the treatment. Thus, treatment strategies of higher complexity intended to overcome or prevent resistance have been proposed as alternatives to current standard-of-care treatments. A class of these complex treatment strategies combines multiple targeted inhibitors, often at lower doses than the maximal tolerable dose. A specific instance of this class of treatment, 'Multiple Low Dose (MLD)' therapy, showed promising results.[1] Typically the design of this class of treatment follows two basic principles: to increase the suppression of an effector-species (e.g. phosphorylated MAPK) and to maximize cell killing. Therefore, combinations are selected based on known or experimentally identified modulators of the effector-species, while dosages are selected based on a phenotypical readout like cell viability. Due to the complex and non-linear regulation to which the effector-species is subjected it can be difficult to understand the relationship between effector-species inhibition, dosages and combinations. Difficulties that contribute to challenges in understanding why and how drugs need to be combined. One way to systematically account for this non-linear regulation is to use computational models. Once a candidate model has been calibrated on multiple perturbation measurements, it can be used to define regions of synergistic or antagonistic effector-species inhibition for different combinations and dosages. This is useful information for dissecting the biological mechanisms behind the efficacy of a given drug combination, and for optimizing concentrations in combination treatments. Here we investigate the inhibition of the EGFR-MAPK pathway with up to four different inhibitors in combination. We focus on this pathway, as MLD was shown to be particularly effective in this pathway. We model the pathway and inhibitor mode of action using mass action kinetics, reduce model complexity using total Quasi Steady State Approximation (tQSSA)[2] and we calibrate the reduced model using statistical approaches. To this end we employ a (phopho-)proteomics dataset collected in PC9 lung cancer cells subjected to a total of 20 MLD combination treatments. The objective of the calibration is to find a shared set of kinetic parameters that map measured intensities to simulated molar concentrations. To calibrate the model we use a two stage calibration approach where total protein abundance are quantified using "Proteomic Ruler"[3] on proteomic Mass Spectrometry (MS) Label Free Quantification (LFQ) data, while other parameters are jointly inferred fitting phospho-proteomics MS LFQ data. We conducted in silico experiments where we investigated how robustly we can recover true solutions under multiple scenarios (e.g. increasing noise, missing perturbations). Beside the methodology and in silico experiments, we will present the latest results of applying the framework to this dataset.

References

1. Fernandes Neto JM, Nadal E, Bosdriesz E, et al. Multiple low dose therapy as an effective strategy to treat EGFR inhibitor-resistant NSCLC tumours. *Nat Commun*. 2020;11(1):3157. doi:10.1038/s41467-020-16952-9
2. Borghans JA, de Boer RJ, Segel LA. Extending the quasi-steady state approximation by changing variables. *Bull Math Biol*. 1996;58(1):43-63. doi:10.1007/BF02458281
3. Wiśniewski JR, Hein MY, Cox J, Mann M. A "proteomic ruler" for protein copy number and concentration estimation without spike-in standards. *Mol Cell Proteomics*. 2014;13(12):3497-3506. doi:10.1074/mcp.M113.037309

Inferring Mobility Reductions from COVID-19 Disease Spread along the Urban-Rural Gradient

Sydney Paltra[1], Jonas Dehning[2], Viola Priesemann[2,3], Kai Nagel[1]

[1]Technische Universität Berlin, Germany; [2]Max-Planck Institute for Dynamics and Self-Organization, Göttingen, Germany; [3]Faculty of Physics, Georg-August-University Göttingen, Germany

The COVID-19 pandemic reshaped human mobility through both policy interventions and voluntary behavioral changes. People postponed social visits, shifted their meetings and shopping online, avoided peak-hour public transport, observed stay-at-home orders, and adapted to school closures. These mobility adjustments limited the number of contacts, reduced infection opportunities, and helped mitigate disease spread. Viewing mobility behavior as a measurable, immediately available indicator of population response, existing research has primarily focused on mobility adjustments at the national level or in selected metropolitan regions, leaving rural areas largely unexplored. At the same time, our understanding of which environmental, social, and demographic factors facilitated mobility reductions and consequently pandemic mitigation remains incomplete. To improve our understanding of the interrelation of mobility behavior and disease spread, we follow a three step approach. First, we introduce a Bayesian hierarchical model to quantify heterogeneity in mobility responses across time and space in Germany's 400 districts using anonymized mobile phone data. We multiplicatively decompose out-of-home duration – our mobility measure – into a disease-responsive component and disease-independent (temperature, school vacations, public holidays) factors. The disease-responsive component combines national and local incidence through a weighted finite-memory signal and allows for pandemic fatigue. This yields a district-specific reaction strength to disease spread. We focus on the period from March 2020 to March 2021, performing Bayesian inference for the parameters of our model using Markov-Chain Monte Carlo (MCMC) sampling. Second, we build a linear model to attribute cross-district variation in decrease in out-of-home duration to population density and demographic and socioeconomic covariates. Third, we present a structural equation model to attribute cross-district variation in peak incidence to the same covariates and additionally to the average decrease in out-of-home duration. The hierarchical model successfully disentangles and quantifies the impact of the disease-responsive and the disease-independent components, inferring the two major decreases in out-of-home duration during the first year of the COVID-19 pandemic: the sharp decline in spring 2020 during the initial COVID-19 wave and the second decline in winter 2020/2021 during the second COVID-19 wave. The course of out-of-home duration is dominated by the influence of the disease-responsive component. During the first wave, the disease factor reduces the out-of-home duration most strongly in the week ending April 19th, 2020, reaching a median multiplicative impact of 0.77, IQR: ([0.73, 0.80]). Despite higher incidences during the winter 2020/2021 wave, the disease factor reduces out-of-home duration less than during spring 2020, reaching a median maximal multiplicative impact of 0.83 (IQR: [0.81, 0.86]). This suggests that pandemic fatigue fully compensates the effect of higher incidences. Temperature and holiday factors provided secondary but consistent reinforcing effects. Analysis of the reaction strength reveals significant differences along the urban-rural gradient, with large cities reducing most strongly. Employment-related variables, i.e. unemployment rate and share of employment sectors with less remote work feasibility, further help explain variance in reaction strength during the first wave, while political variables gain significance during the second wave. However, the structural equation model reveals that reduced mobility only partially translates to lower peak incidence, indicating other factors remain influential. Overall, our results advance our knowledge of factors that drive mobility reductions and highlight the potential of mobility behavior as an operational proxy for population response.

PEtab SciML: The missing layer for scalable and flexible scientific machine learning modeling in biology

Sebastian Persson, Fabian Fröhlich

The Francis Crick Institute, London, UK

Dynamic, mechanistic ordinary differential equation (ODE)-based models are a powerful tool for studying cellular pathways. For example, this modeling approach has been used to study processes ranging from gene expression, to signaling over apoptosis. However, dynamic mechanistic models have limitations. Their predictive power is constrained by gaps, biases, and inconsistencies in the literature. Moreover, they typically require quantitative time-lapse data that is time-consuming to collect for training, and although training would benefit from integrating other modalities such as omics and patient metadata, doing so remains an open challenge. Conversely, purely data-driven machine-learning models lack interpretability and require extensive training data. Hybrid scientific machine learning (SciML) models aim to address these shortcomings by combining interpretable mechanistic ODE modules with data-driven modules. While still emerging in biology, SciML models have shown strong performance in modelling complex systems in other fields, such as weather dynamics. Despite its potential, adoption of SciML modeling in biology is limited by insufficient infrastructure. Particularly, dedicated software packages are needed because coding end-to-end-differentiable SciML problems for state-of-the-art gradient-based model training (parameter estimation) is technically non-trivial. In addition, model exchangeability is hampered by the absence of a standardized, reproducible format for specifying SciML training problems, analogous to the PEtab standard for mechanistic ODE models. To address these gaps, we have developed the PEtab-SciML extension to the PEtab format and implemented support for it in established gradient-based modeling toolboxes: the Julia package PEtab.jl and the Python-based AMICI package. Here, we will present the PEtab-SciML data format and demonstrate how it mitigates current limitations of mechanistic modeling. Using real-data examples, we will show how PEtab-SciML enables integration of diverse data modalities into model training by supporting model setups where a machine-learning module takes context data (e.g., multi-omics, protein sequence) as input and output kinetic/model parameters of an ODE model. We also show how PEtab-SciML supports machine-learning-based “black-boxing” of complex expressions (e.g., quarantine strength in an SIR model) within the ODE model equations. Finally, we will present benchmarks comparing SciML training performance between Python and Julia ecosystems. In summary, PEtab SciML provides a reproducible, user-friendly, and flexible infrastructure for SciML modeling.

Mathematical Modeling of RNA Velocity Manifold Dynamics Identifies Immune–Metastatic State Transitions and Tertiary Lymphoid Structure Stability Landscapes in Hepatocellular Carcinoma

Prihantini Prihantini[1], Rini Winarti[2], Rifaldy Fajar[1]

[1]AI-BioMedicine Research Group, IMCDS-BioMed Research Foundation, Indonesia; [2]Department of Biology, Yogyakarta State University, Indonesia

Background: Single-cell RNA sequencing captures cellular heterogeneity at high resolution, but static analyses overlook the continuous, directionally evolving state transitions that underlie cancer progression. In hepatocellular carcinoma, the shift from tertiary lymphoid structure–rich immune-inflamed states to metastatic phenotypes such as portal vein tumor thrombus or lymph node involvement reflects coordinated dynamics embedded within the single-cell manifold. A velocity-informed mathematical framework is required to quantify transition rates, define metastable attractors, and assess how signaling pathway perturbations reshape these immune–metastatic trajectories with clinical relevance. Methods: We analyzed single-cell RNA sequencing datasets from the Gene Expression Omnibus (GEO: GSE149614, GSE140228, GSE125449) covering non-tumor liver, primary hepatocellular carcinoma, portal vein tumor thrombus, metastatic lymph node, and immune compartments, and integrated them with bulk transcriptomes and clinical outcomes from TCGA-LIHC ($n = 343$). A unified manifold was built using Seurat v5, and velocity fields (scVelo) generated a directed transition graph. Macro-states were defined as attraction regions on the velocity-informed manifold, yielding five attractors: non-tumor, tertiary lymphoid structure–high immune-inflamed, tertiary lymphoid structure–low immune-cold, portal vein tumor thrombus, and metastatic lymph node. A continuous-time Markov generator matrix was estimated from velocity-derived transitions, with pathway activities (interferon, transforming growth factor beta, angiogenesis, exhaustion) modulating transition intensities. Spectral decomposition identified eigenvectors, mean first passage times, and a tertiary lymphoid structure stability margin. Bulk TCGA-LIHC transcriptomes were deconvolved into attractor proportions for a metastatic progression index, and pathway perturbation experiments simulated the effects of 30% transforming growth factor beta inhibition or 20% interferon enhancement. Results: RNA velocity–directed flows, with tertiary lymphoid structure–high attractors comprising 24.3% of all cells (IQR 17.8–33.6%), portal vein tumor thrombus attractors 19.4% (IQR 11.2–27.9%), and metastatic lymph node attractors 8.7% (IQR 4.1–15.3%). Velocity-constrained modeling eliminated 61.8% of implausible transitions and produced a generator matrix with a tertiary lymphoid structure stability margin of 0.39 (95% CrI 0.31–0.47). A 1 SD increase in transforming growth factor beta activity accelerated transitions from tertiary lymphoid structure–low to portal vein tumor thrombus states by 2.4-fold (95% CrI 1.8–3.2), while interferon signaling reduced this transition rate by 41% (HR 0.59; 95% CrI 0.46–0.76). The mean first passage time from tertiary lymphoid structure–high states to metastatic basins was 18.2 months (95% CrI 13.4–23.7; coefficient of variation 37%). When projected to TCGA-LIHC, the metastatic progression index stratified 3-year recurrence into low-, intermediate-, and high-risk groups at 22.1%, 44.8%, and 69.5% ($p < 0.0001$), with AUROC 0.83 (95% CI 0.79–0.87) and calibration slope 0.91 (95% CI 0.83–0.97). Simulated transforming growth factor beta inhibition increased immune-inflamed attractor stability by raising mean first passage time by 40.8% (95% CrI 28.7–52.3%), while interferon enhancement reduced high-risk classification from 32.4% to 18.9% and improved predicted 3-year survival by 13.6%. Conclusions: This velocity-informed single-cell framework formalizes immune–metastatic progression in hepatocellular carcinoma as a dynamical system with quantifiable attractors and transition operators. Tertiary lymphoid structure stability emerges as a key metastability property derived from cell-state geometry, and pathway-specific perturbation modeling provides mechanistically supported, clinically relevant strategies for influencing metastatic trajectories.

A population model reveals a surprising role of stochastic cell division in epigenetic memory systems

Viviane Klingel[1], Dimitri Graf[2], Sara Weirich[2], Albert Jeltsch[2], Nicole Radde[1]

[1]University of Stuttgart, Institute for Stochastics and Applications, Germany; [2]University of Stuttgart, Institute for Biochemistry, Germany

Epigenetic memory systems store transient environmental signals in bacteria as specific DNA methylation patterns. The synthetic zinc finger protein (ZnF4) binds to the DNA in a methylation-dependent manner and represses the expression of the DNA methyltransferase CcrM. The mechanisms ensuring long-term stability of the ON-state remain unclear. Measurements showed a gradual shift of cell populations from ON to OFF starting after about four days of cultivation. We use a hybrid modeling approach that integrated flow cytometry data and bulk DNA methylation measurements to test the hypothesis that stochastic cell division is a key factor in this transition. Interestingly, model parameters cluster into two groups with opposite effects of cell division rates on ON-state stability. Experiments show that faster cell division increases memory stability—an initially unexpected and surprising result. Model simulations provide a potential explanation for this observation on the molecular level and deepen our understanding of the mechanisms and timing of the ON/OFF switch in individual cells.

Critical dynamics generates slow manifolds for timing in neural networks

Gayathri Ramesan

Gayathri Ramesan, Max Planck Institute for Neurobiology of Behavior — Caesar, Bonn, Germany

Current theoretical frameworks for neural computations rely on attractor-based formalisms such as line attractor, ring attractor etc. However, in reality, any biological entity encounters dynamic environments, implying that the potential landscape of the system is continuously changing, likely hindering asymptotic convergence to stable states. In response to a continuously changing environment, biological computations performed must be stable enough to retain previous information, while simultaneously remaining flexible to integrate new information. These features suggest an alternative framework for neural computation, in which trajectories do not settle on attracting sets of lower dimension but evolve non-asymptotically under the influence of dynamically slow regions, replacing the classical notion of attractors. This would further ensure that computations remain flexible and responsive, as trajectories are continuously maintained away from attractors. Recently, alternative dynamical objects for computation that does not rely on (un)stable attractors but rather on transiently stable phase-space flows such as ghost channels and ghost cycles have been proposed.

To investigate the significance of such transients further, we study minimal recurrent neural networks (RNNs) trained on complex temporal tasks and utilise dynamical systems theory to understand the encoding of information. One example is a working memory task, in which the system is trained to reproduce the time interval between two past events upon receiving a cue. We utilise an objective function representing the kinetic energy of the system to identify the network’s solutions and further characterise them based on the associated eigenvalues. Previous studies have hypothesised that time intervals are encoded by trajectories converging to approximate line-attractor dynamics. We observe that the trained networks utilise a diverse set of dynamics to solve the task across different training realisations, however, they encode temporal intervals by directing the system's trajectories through a set of transiently stable slow points as a general theme. We aim to understand how the generated slow-point set enables the RNNs to generalise across a range of time intervals, potentially serving as a foundation for studying on-the-fly learning in natural systems..

Backward bifurcations and multistationarity

Alan Rendall[1], Alexis Nangue[2]

[1]Institut für Mathematik, Johannes Gutenberg-Universität Mainz, Germany; [2]Higher Teachers Training College, University of Maroua, Maroua, Cameroon

The theory of backward bifurcations provides a criterion for the existence of positive steady states in epidemiological models with parameters where the basic reproductive ratio $\mathcal{R}_0$ is less than one. It is often seen in simulations that this phenomenon is accompanied by multistationarity, i.e. the existence of more than one positive steady state, but the latter circumstance is not implied by the general theory. In this work we proved a theorem which gives a criterion for the existence of one stable and one unstable positive steady state for parameters where $\mathcal{R}_0$ is either less than one or greater than one. These steady states arise in a bifurcation and it will be explained how the ideas of this theorem are related to universal deformations of transcritical bifurcations. As an example it is shown that this theorem can be used as a basis for showing the existence of parameters for which there are two positive steady states, one of which is stable, in a model for the in-host dynamics of hepatitis C.

Geometry, timescales and boundaries affect aggregation-based patterning in multicellular systems

Jan Rombouts[1], Michael Zhao[2], Alexander Aulehla[2], Anna Erzberger[2]

[1]Université Libre de Bruxelles, Belgium; [2]EMBL Heidelberg, Germany

Understanding how embryonic cells form structured patterns is an important goal of developmental biology. Here, I will discuss how we combined experimental and mathematical approaches to understand the effect of domain geometry on pattern formation. We used primary cells from mouse embryos that, after dissociation, are able to self-organize into spatial patterns. We show that there is a large role for cell movement in the formation of these patterns and corroborate this with a simple nonlocal continuum model. To study the effect of domain size on patterns, we developed analytical and numerical tools to extend our theory to short bounded domains. By pairing these theoretical results with experiments in which we manipulate the size of the cell seeding domains, we show how the patterns are controlled by domain size, timescales and boundary interactions.

Understanding When Lotka–Volterra Models Fail in Microbial Community Analysis

Saeed Salehi[1,2], Satyajeet Sheetal Bhonsale[2], Jan F. M. Van Impe[2], Eva Balsa-Canto[1]

[1]Biosystems and Bioprocess Engineering Group, Bio2Eng, IIM-CSIC, Vigo, Spain; [2]BioTeC+, Chemical and Biochemical Process Technology and Control, KU Leuven, Ghent, Belgium

Microbial communities regulate critical processes in soil, environment, food fermentation, and human health, with promising applications in biotechnology. Understanding species interactions is essential for designing functional microbial consortia, yet inferring interaction types from experimental data remains challenging. Generalized Lotka–Volterra (gLV) models remain widely used for this task, but recent studies have exposed substantial limitations in their reliability. Crucially, it is still unclear under which biological or experimental conditions gLV models fail, and to what extent these failures stem from practical identifiability issues or limitations of the gLV formalism to represent underlying mechanisms. This lack of systematic understanding limits both experimental planning and informed model choice for microbial community analysis. We present a comprehensive computational study of two-species microbial systems, generating synthetic growth data from mechanistic Monod kinetics under diverse interaction scenarios: resource partitioning (no interaction), competition for shared substrates, affinity-mediated competition, toxin-mediated inhibition (amensalism), and both essential and non-essential cross-feeding facilitation. Systematic gLV parameter estimation was performed under varying levels of measurement noise (0–10%), sampling density (10–20 points), death-phase dynamics, and experimental designs including single co-cultures, multiple co-culture experiments, and monocultures. Across all scenarios, fitting gLV models solely to single co-culture datasets produced unreliable inferences: interaction signs were frequently incorrect, confidence intervals typically exceeded 100%, and biologically implausible parameter estimates emerged. These failures reflect severe practical identifiability problems stemming from insufficient experimental diversity. Integrating monocultures alongside multiple co-cultures largely resolved these identifiability issues across simple interaction types. For non-interacting species, interaction parameters could be confidently fixed to zero with strong statistical support and dramatically reduced uncertainty. Co-cultures alone, in contrast, routinely generated spurious interactions with wide confidence intervals and incorrect ecological conclusions—an explicit demonstration of how poor practical identifiability, not biological interaction, can drive false positives. However, even multi-experiment schemes could not provide reliable parameter inference for all scenarios. Some systems involving toxin-mediated amensalism or cross-feeding facilitation retained persistent uncertainties or inconsistent interaction signs, even when monocultures and multiple co-cultures were combined. These cases displayed intrinsically weak and poorly identifiable effects, revealing fundamental limitations of the gLV formalism to capture mechanistic processes such as toxin accumulation, nonlinear metabolite exchange, or dynamically regulated cross-feeding. Together, these results demonstrate that while appropriate experimental design can overcome identifiability-driven failures and prevent wrong ecological conclusions in many interaction types, gLV models remain intrinsically unable to recover complex biological mechanisms such as toxin effects and cross-feeding. This work provides practical guidelines for experimental planning and clarifies when gLV models are applicable, and when mechanistic or time-dependent modeling frameworks are required to faithfully infer microbial interactions.

A regularized Cox model for selecting interactions and time-varying covariate effects

Alina Schenk[1], Anna-Lena Kuenster[1,2], Matthias Schmid[1]

[1]Institute for Medical Biometry, Informatics and Epidemiology, Medical Faculty, University of Bonn, Bonn, Germany; [2]Department of Mathematics, Informatics and Technology, Koblenz University of Applied Sciences, RheinAhrCampus Remagen, Remagen, Germany

Introduction: The Cox proportional hazards model is a widely used method for analyzing clinical time-to-event data. In its standard form, the Cox model assumes that the covariate effects on the hazard function are constant over time. However, in many clinical settings, covariate effects may vary with time, and covariate interactions may significantly influence survival. Selecting interactions and time-varying effects within the Cox model framework may be challenging and often requires pre-screening followed by model selection steps. These selection steps are often carried out through automated stepwise procedures, which, however, can be unstable—particularly when a large number of potential effects are considered.

Methods: We introduce a linked-shrinkage adaptive elastic net procedure for selecting two-way interactions and time-varying effects in Cox models.[1,2] The method combines an adaptive elastic net framework with penalties estimated in a preceding main-effects-only ridge regression. The method considers time-varying effects as piecewise constant functions. Linked-shrinkage is used for the specification of the penalty weights for interaction and time-varying effects by taken the corresponding main effects into account. Penalty weights are specified such that time-varying effects and interaction effects are penalized more strongly compared to main effects. We assessed the proposed modeling approach through a simulation study based on Weibull-distributed survival times, incorporating various structures of time-varying covariate effects. With the help of the simulation study we compared the proposed method with several established methods, such as the classical elastic net extended to the Cox model. For comparison, the performance was evaluated based on mean squared error of predicted survival probabilities and selection accuracy.

Results: The proposed method reliably identified true time-varying and two-way interaction effects, with false positive rates below 2% for time-varying coefficients. Sensitivity ranged between 85%–90% and 92%–96%. Compared to standard regularized Cox models, the proposed method yielded better performance and the ability to select informative main/interaction/time-varying effects in a more precise way. Furthermore, we illustrate the proposed approach by analyzing real-world data from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) program.[3]

Conclusion: By addressing the limitations of manual covariate selection and stepwise procedures, the proposed method extends penalized estimation techniques to Cox regression with time-varying coefficients. Further, it facilitates the simultaneous selection of relevant interaction terms and time-varying covariate effects.

Keywords: Adaptive elastic net, Cox model, interactions, linked-shrinkage, regularization, time-varying covariate effects

References

1. van de Wiel MA, Amestoy M, Hoogland J. Linked shrinkage to improve estimation of interaction effects in regression models. *Epidemiol Methods*. 2024;13(1):20230039. doi:10.1515/em-2023-0039
2. Zou H, Hastie T. Regularization and variable selection via the elastic net. *J. R. Stat. Soc., B: Stat. Methodol*. 2005;67:301–320. doi:10.1111/j.1467-9868.2005.00503.x
3. National Cancer Institute. Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat Database. https://www.seer.cancer.gov. Accessed: 2025-10-05

Mathematical Modeling of Persistent Treatment Responses After Targeted Radiotherapy in Cancer

Lara Schmalenstroer[1], Russell C. Rockne[2], Farnoush Farahpour[1,3]

[1]University of Duisburg-Essen, Germany; [2]Division of Mathematical Oncology, Department of Computational and Quantitative Medicine, Beckman Research Institute, City of Hope National Medical Center, Duarte, CA, USA; [3]Institute for Cell Biology (Tumor Research), University Hospital Essen, Germany

Solid tumors, such as pancreatic or lung cancer, are major causes of cancer-related deaths worldwide. Despite the availability of multiple treatment options including radiotherapy or chemotherapy, long-term survival rates of patients with solid tumors remain low due to the development of treatment resistance and tumor recurrence. In recent decades, targeted therapies have emerged as a promising approach to address these challenges. Targeted radiotherapy (TRT) is a type of radiotherapy that uses radiolabeled molecules – typically antibodies or other small molecules – to selectively deliver radiation to cancer cells while minimizing damage to healthy tissue. The therapeutic window and efficacy of TRT depend on factors such as the radioligand's decay rate, the cells' radiosensitivity, drug binding kinetics, DNA damage repair mechanisms, and the biological clearance of the drug. A critical open question is how these biological and physical processes jointly shape tumor response over time. Experimental studies have shown that irradiation not only causes immediate DNA damage but also induces persistent shifts in tumor growth kinetics, underscoring the importance of understanding both short- and long-term responses to irradiation. Computational modeling offers a powerful way to complement experimental studies by integrating biological complexity and treatment variables in a quantitative framework, enabling systematic testing of hypotheses that are difficult to address experimentally. While the common approach to modeling radiation responses, employing the linear-quadratic model and its derivatives to compute the survival fraction, has been successful in describing the overall impact of radiation on a cell population, it is not suitable for capturing dynamic, persistent, and long-term treatment effects in a population of adaptive cells, as it disregards the role of heterogeneity and plasticity in the response. We developed a phenomenological partial differential equation-based model that integrates both immediate and delayed radiotherapy effects by incorporating these two important features of living cells. A central aspect of our model is the inclusion of probabilistic proliferation dynamics, where cancer cell proliferation rates serve as the primary determinant of radiosensitivity, consistent with the well-established hypothesis that highly proliferative cells are more radiosensitive than slower proliferating cells. By using these proliferation rates to determine the rate of cell death after irradiation, the model predicts a heterogeneous cancer cell killing rate, where the proliferation rate determines the type of response. This results in a dynamic and adaptive composition of the tumor. While slowly proliferating cells are most affected at the onset of treatment, highly proliferative cells exhibit a delayed response, with the strongest treatment-induced cell death occurring approximately seven days after the onset of radiotherapy. Thus, the model provides insights into relapse dynamics and heterogeneous treatment responses, as well as the relationship between proliferation rate and radiosensitivity. The model moves beyond survival fraction-based approaches by capturing dynamic and persistent changes in growth kinetics and integrating treatment-induced alterations following radiotherapy. This framework enables the systematic exploration of how parameters such as radiosensitivity, antibody binding and clearance, and DNA damage repair mechanisms jointly influence tumor control. To ensure biological relevance, ongoing work focuses on experimental validation in collaboration with experimental partners. The model has been fitted to data from preclinical studies involving TRT in mice with induced lung tumors, providing a quantitative link between experimental observations and model predictions. The ultimate goal is to guide the design and optimization of targeted radiotherapy and potential combination strategies.

The influence of the mutation process on the long-term behavior of infectious diseases

Marvin Schulte[1,2], Jan Mohring[1], René Pinnau[2]

[1]Fraunhofer Institute for Industrial Mathematics ITWM, Kaiserslautern, Germany; [2]RPTU University Kaiserslautern-Landau, Germany

Mechanistic infectious disease models play a crucial role in evaluating the impact of public health strategies during an epidemic. In the Covid-19 pandemic, the rise of new infection waves corresponding to the emergence of new variants showed the need of incorporating the effects of multiple virus variants into these models. A new variant can have characteristics that influence transmissibility, severity, and the effectiveness of pre-existing immunity. However, traditional models often account for existing variants without capturing the dynamical nature of the mutation process itself. Understanding the interplay between transmission and mutation dynamics is essential for investigating the long-term behavior of infectious diseases characterized by frequent mutations, such as Covid-19 and influenza. In our research, we use a compartmental multi-variant model that covers the effects of partial immune escape. This model is extended by a stochastic representation of the mutation process, which is chosen as an inhomogeneous Poisson process. The intensity function governing the occurrence of new mutations is chosen proportional to the fraction of infectious individuals, representing the viral load in the population. This proportionality constant is called the mutation rate. Hence, the transmission dynamics and the mutation process interact with each other. This interplay is mathematically described as a stochastic hybrid system. We consider models with and without seasonality. In our presentation, we will introduce the novel framework modeling transmission and mutation simultaneously. We will explore under which conditions a mutating virus can persist within a population. Our focus will be on a sensitivity analysis for key parameters that influence the long-term behavior of our model. These include the mutation rate, the basic reproduction number and the level of partial immune escape, respectively the parameters characterizing their distributions for novel variants. Our findings also reveal that there exists a time interval between the emergence of new variants that maximizes the number of total infections. Finally, we will give a brief outlook on how this model can be applied to optimization problems in public health.

Geometric Modeling of Developmental Velocities in Single-Cell Data

Stanislaus Stein[1], Simon Anders[1#], Evelyn Herberg[2#], Roland Herzog[2#]

[1]BioQuant, Heidelberg University, Germany; [2]IWR, University of Heidelberg, Germany

[#]shared last authorship

Single-cell sequencing provides static snapshots of inherently dynamic processes. Trajectory inference aims to reconstruct the developmental paths from the dataset. Classical methods such as principal curves or diffusion pseudotime rely on Euclidean distances in high-dimensional space, which become unreliable due to the curse of dimensionality. Moreover, these approaches provide only an ordering of cells, not a meaningful notion of velocity. Under ergodicity, all intermediate states exist within the sample, allowing developmental progress to be modeled as a regression on the data manifold. As biological processes happen on different timescales, some transitions occur faster and are thus less sampled. The resulting density imbalance implies that trajectories should advance quickly through low-density regions and slowly through high-density ones. Recent work in statistical geometry has proposed to reframe regression curves as geodesics w.r.t. the so-called Fermat metric, a conformal metric $\mathrm{g_x}(\mathrm{u},\mathrm{v}) = \frac{\langle \mathrm{u},\mathrm{v}}{(\log \mathrm{p}(\mathrm{x}))^{\beta}}$ on a Riemannian manifold where $\log \mathrm{p}\,(\mathrm{x})$ is the log likelihood at x and $\beta \in \mathrm{R}$ a hyperparameter. For a positive β, geodesics w.r.t. the Levi-Civita connection become a sort of regression, as distances are short where the log likelihood is high. Thus, a length-minimizing geodesic will stick to where the data is. Solving the associated geodesic equation requires a density estimate for initialization and a score estimate for a relaxation. It has been demonstrated that these regression lines are more stable than the Euclidean distance-based principal curves. We have extended this framework in two critical ways. First, in previous work the density and score estimate were estimated using separate neural networks. A diffusion model based on stochastic differential equations, however, can provide both a score estimate and a density estimate, the latter via the associated Fokker-Planck equation. This allows us to unify the model into one neural network circumventing the need to train a likelihood-based normalizing flow, thus reducing overall compute. Second, we can uniformly resample curves with respect to the length functional, which depends on the metric and thus on β. This gives us direct control over the velocity of the resampled curve. For a negative β the curve will slow down in high-density areas and vice versa. This allows us to reparameterize arbitrary curves such that their velocity changes according to the density. We can thus model the hypothesized relationship between data density and developmental velocity: regions with sparse sampling (low density) correspond to faster transitions, while densely populated regions correspond to slower progression along the trajectory. We constructed a purpose-build autoencoder that works on single-cell mRNA data and projects the data into a latent space. We train a diffusion model on this latent space giving us access to both score and density estimates. We use these estimates to solve the geodesic equation w.r.t. the Fermat metric and reparameterize with a negative β to derive meaningful velocities. To benchmark, we apply the method to datasets with multiple time-points, allowing us to compare the progression of our curve's pseudotime with the actual wall-clock time. This work outlines a geometric framework that links score-based generative modeling with trajectory inference in single-cell analysis. Unlike conventional pseudotime methods that provide only an ordering of states, the geodesic formulation yields trajectories with interpretable velocities, enabling the recovery of relative dynamical rates across the data manifold. Although the current implementation is limited by sparse sampling of transitional states, it establishes the basis for consistent estimation of developmental timescales and a clearer quantitative link between statistical geometry and biological dynamics.

Detecting changes in protein-covariation in smooth cell-state changes

Tim Stohn[1], Evert Bosdriesz[1], Lodewyk Wessels[2]

[1]Vrije Universiteit Amsterdam, The Netherlands; [2]Netherlands Cancer Institute, Amsterdam, The Netherlands

Standard single-cell analyses typically rely on clustering, e.g. to define discrete cell states, before downstream analyses like studying correlations or inferring regulatory interactions. However, cellular phenotypes often form continuous manifolds, with cells stransitioning smoothly between cell states or even types, and clustering imposes artificial boundaries neglecting gradual changes in molecular relationships. We introduce LoCo (local correlation analysis), a framework for detecting smooth, local variations in correlation structure across the single-cell-state space. While the approach is in principle applicable to any single-cell modality, we have so far focused on single-cell protein data, as this modality provides the closest readout of the signalling networks we aim to study. By examining local changes in protein–protein correlations across the single-cell-state space, we seek to understand how alterations in protein interactions drive signalling dynamics, cell-state transitions, and responses to drug treatment. Instead of relying on prior clustering, LoCo first constructs local neighborhoods of phenotypically similar cells by grouping cells that are close in single-cell space (or any user-defined embedding, e.g. only using cell-state markers). It then builds a neighborhood graph by connecting nearby neighborhoods and computes all pairwise feature correlations within each neighborhood, yielding a local correlation profile for every feature pair. These local correlation patterns are ranked using a graph-based Laplacian score, which prioritizes correlations that vary strongly across the neighborhood graph while remaining spatially coherent. This framework enables the identification of state-specific, continuous shifts in correlation structure—signals that are typically obscured by global analyses and cannot be captured by clustering-based approaches. We first applied LoCo to simulated single-cell protein data and found that it robustly recovers cell-state–specific correlations that would be missed by global analyses. We then applied LoCo to single-cell proteomic measurements of cells treated with increasing doses of an EGFR inhibitor. LoCo identified dose-dependent shifts in correlation structure within the MAPK pathway. As expected, low-dose perturbations left upstream correlations largely unchanged, however, higher doses reduced correlations among upstream components and surprisingly increased correlations downstream in the pathway. Notably, many of these correlation patterns vary smoothly across the single-cell landscape—individual doses contain cells spanning multiple regimes of pathway activity—highlighting that clustering cells solely by inhibitor dose would obscure the continuous nature of these correlation changes. LoCo provides a simple framework for analyzing locally varying correlation structures in single-cell data and offers a principled alternative to cluster-based analysis of correlations in heterogeneous cell populations. LoCo could detect correlations that might otherwise go unnoticed as they appear only in a subset of cells. Additionally, it could be used in prior data analysis to help define clusters driven by correlation changes rather than absolute feature abundance to group cell with similar ‘signalling activity’. As such we hope that it can be used in combination with network reconstruction methods to gain deeper unsterstanding of cell-state specific signalling dynamics.

Integration of proteomics data from cell lines and tumors to profile patient drug sensitivity

Cong Quan Ta[1,2], Ursula Klingmüller[2], Andreas Raue[1]

[1]University of Augsburg, Germany; [2]German Cancer Research Center, Heidelberg, Germany

Preclinical cancer research often relies on cancer cell lines because they are more accessible than patient-derived tumors. However, drug responses observed in cell lines frequently do not translate into similar outcomes in patients. Thus, accelerating the drug development process would greatly benefit from identifying which cell lines best represent patient drug sensitivity. High-throughput omics technologies, such as transcriptomics and proteomics, provide a promising foundation for this goal by enabling comprehensive molecular profiling of both tumors and cell lines. However, biological and technical differences between these systems make direct comparisons challenging, which raises the need for methods that can remove confounding variation while preserving relevant biological information. Several integration approaches were developed for transcriptomic data, yet drug response is largely determined by protein activity. Thus, integrating proteomic data could improve the alignment of drug sensitivity profiles between cell lines and patients. Despite significant progress in mass spectrometry-based proteomics, technical variation remains prevalent across studies and quantification methods. To address these challenges, we developed a deep learning method designed to remove technical variation across proteomic datasets. We showed that commonly used batch correction tools and deep learning methods designed for transcriptomic data can remove relevant biological information in the proteomic data. We applied our method to four pan-cancer proteomic datasets generated using tandem mass tag and label-free quantification, demonstrating effective removal of study-specific batch effects. These four datasets, which include two cell line and two cancer patient cohorts, also allowed us to show that our method reduces system-level confounding variation to reliably integrate cell line and tumor proteomes. This integration provides a foundation for more informed preclinical model selection and may improve the translational relevance of future cancer drug discovery studies.

From Classrooms to Communities: Modeling the Impact of School-Based Interventions for Future Pandemic Response

Alexandra Teslya[1], Zicheng Fang[2], Büşra Atamer Balkan[2], Clarize De Korne[1], Matthijs De Winter[3], Lucie Vermeulen[3], Quirine Ten Bosch[1], Patricia Bruijning-Verhagen[1], Ganna Rozhnova[1]

[1]University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands; [2]Wageningen University & Research, Wageningen, The Netherlands; [3]National Institute of Public Health and the Environment (RIVM), Bilthoven, The Netherlands

Introduction In the context of respiratory pandemics, schools are a critical setting: while their high-contact environments can amplify community transmission, they remain indispensable for children's learning and wellbeing. As a part of pandemic preparedness for emerging respiratory pathogens, the RE-PASS project presents a novel multi-scale modeling framework to support the development of school-based interventions that balance infection control with minimizing the loss of learning outcomes by capturing both the complexity of transmission dynamics and the social consequences of epidemic spread and mitigation strategies. Methods The modeling framework captures transmission across three interconnected scales: (1) within-classroom dynamics, mimicking daily movement and interaction patterns of students and teachers; (2) within-school transmission, mediated by shared staff and cross-group connections; and (3) a school-community network linking households, schools, and the community. Epidemiological state of all individual agents (students, teachers) is tracked on a day-to-day basis, including a time-dependent virus shedding profile. The framework will be demonstrated using empirical SARS-CoV-2 data at the initial stages of the outbreak in the Netherlands when pharmaceutical interventions, such as vaccines, were not yet available. The synthetic school-household network is based on Dutch data and incorporates socio-economic stratification at the school-community level. Results Our modeling framework can simulate community outbreaks of diverse respiratory pathogens and evaluate school-based interventions that act at different levels of the system. Despite the high-resolution, the framework is computationally efficient due to a novel approach which leverages precomputed look-up databases. Beyond standard epidemiological outcomes (infections and hospitalizations), the model tracks educational outcomes such as in-person learning days lost and projected learning loss. These outputs support trade-off analyses between pandemic control and educational continuity. Conclusion Our work lays the foundation for policy-relevant modeling of school-based interventions in future respiratory pandemics. By explicitly representing transmission at classroom, school, and community levels, and by quantifying both health and societal impacts, the framework aims to inform preparedness strategies that are effective, equitable, and context-dependent.

What Does the Shape Space of T-Cell Epitopes Look Like?

Johannes Textor

Radboud University, Nijmegen, The Netherlands

How can we predict if a given antigen will elicit a robust immune response in most people? This is an important question for the design of (non-personalized) vaccines or when the likely impact of the next influenza strain needs to be gauged. Such predictions are usually based on comparing a candidate epitope to other epitopes with known immunogenicity. For example, an epitope very similar to a known, strongly immunogenic one would also be considered to be immunogenic. Such comparisons are based on the implicit, but largely untested assumption that cross-reactive recognition of TCRs correlates to some measure of sequence similarity. In other words, the landscape of pMH immunogenicity should be smooth - where small sequence alterations should largely correspond to small changes in immunogenicity - rather than rugged - where small changes to the pMHC sequence have largely unpredictable effects on immunogenicity. We first consider theoretical arguments for both scenarios and then re-analyze published TCR-pMHC interaction data to determine the current level of support for either scenario. We find evidence for an intermediate scenario where many similar pMHC are recognized by the same T-cells but where there also exist very dissimilar clusters of sequences that are recognized by the same TCR. We conclude with a discussion of which experimental data would be required to conclusively determine the nature of the pMHC immunogenicity landscape.

MultiNSDEs: Dose-Guided Neural SDEs for Simulating Real and Counterfactual Patient Trajectories

Diego Valderrama

Department of Bioinformatics, Fraunhofer Institute for Algorithms and Scientific Computing (SCAI), Sankt Augustin, Germany

Randomized controlled trials (RCTs) remain the gold standard for evidence generation in clinical research. However, they face several limitations, including high costs, long durations, and frequent recruitment challenges, particularly when longitudinal and multimodal data are required. Emulating clinical trials by generating synthetic subjects to simulate counterfactual outcomes, for example through synthetic control arms, represents a promising strategy to de-risk trial design and paves the way toward the realization of digital twins. Building on our previously published MultiNODEs, our proposed model architecture, Multimodal Neural Stochastic Differential Equations (MultiNSDEs), allows the integration of multiple data sources with heterogeneous temporal resolutions, enabling the generation of realistic longitudinal trajectories for both continuous and categorical variables. It effectively handles missing observations and captures the multimodal interactions inherent in complex clinical datasets. Drug information is incorporated to guide the MultiNSDE in learning patient trajectories. Importantly, MultiNSDEs supports counterfactual simulations, allowing the estimation of what patient outcomes might have been under alternative treatment scenarios. This dual capability, creating synthetic control arms and simulating hypothetical interventions, offers a powerful tool for generating trial-ready synthetic cohorts and evaluating treatment effects without conducting additional interventional studies, thereby supporting evidence generation. To demonstrate the applicability and robustness of MultiNSDEs, we applied the model to two distinct clinical datasets. First, we consider the Anti-Amyloid Treatment in Asymptomatic Alzheimer's (A4) study, a longitudinal study of individuals at risk for Alzheimer's disease, Second, we evaluate the model on the Pooled Resource open-Access ALS Clinical Trials (PRO-ACT) database, which comprises longitudinal data from amyotrophic lateral sclerosis (ALS) clinical trials. These datasets exemplify the diversity of variable types, and temporal structures that MultiNSDE is designed to handle. Model predictions accurately reproduced the empirical data distributions, demonstrating high fidelity across both continuous and categorical variables in training and test subsets. This performance remained consistent across two distinct datasets, A4 (Jensen–Shannon Divergence = 0.17 ± 0.08) and PRO-ACT (0.09 ± 0.15), underscoring the robustness and generalizability of the proposed framework to heterogeneous clinical data structures. Furthermore, the counterfactual simulations 1) treated patients simulated as if they had received placebo, and 2) placebo patients simulated as if they had received treatment, successfully captured the temporal dynamics of treatment effects. The model effectively learned and reproduced the shifts in longitudinal trajectories associated with each intervention, generating synthetic distributions that closely matched those observed in the patients that resemble the real scenarios. Importantly, the average treatment effect (ATE) estimated from synthetic data generated by MultiNSDE, along with its confidence interval, agreed with the predictions obtained from a conventional double-robust estimate derived from the real data. This alignment provides additional evidence of the model's causal validity. Together, these findings demonstrate that MultiNSDE can accurately model treatment effects and generate realistic cohorts, supporting the construction of synthetic control arms and advancing the broader application of synthetic data in clinical research.

Mapping cellular states over time using a hierarchical feature expectation maximization approach for Gaussian mixture modeling

Nadine van de Brug[1,2], Bram Thijssen[1], Evert Bosdriesz[2], Lodewyk Wessels[1]

[1]The Netherlands Cancer Institute, Amsterdam, The Netherlands; [2]Vrije Universiteit Amsterdam, The Netherlands

Individual cells can be in different states, which affects how the cell responds to drugs or perturbations. Understanding these cellular states and the mechanisms driving the transitions between them is essential for improving treatment outcomes. By inferring state transition trajectories, we can design strategies to guide cells towards more responsive states. In this project, we focus on how variability in cellular signaling impacts drug responsiveness, where the state space is shaped by (phospho) protein levels. Measurement technologies to quantify cellular diversity at the phospho protein level in single cells are often destructive and thus cannot track individual cells over time. Instead, these technologies yield unpaired single-cell distributions at discrete timepoints following drug perturbation. To infer state transition trajectories, these distributions can be aligned with methods like Optimal Transport (OT), which maps individual cells or regions of cell state space to their most probable counterparts at later time points. However, applying OT to model dynamic transitions over time – particularly when time steps vary in size and different features evolve at distinct rates – remains challenging. OT inherently assumes gradual state transitions, penalizing large shifts as high-cost transitions. Consequently, it tends to favor smooth trajectories between states with similar protein abundances, potentially overlooking natural dynamics inherent in biological processes. For instance, due to the natural progression of the cell cycle, a cell with high Cyclin B levels is unlikely to maintain such high levels after eight hours. In practice, certain proteins fluctuate within a single experimental interval, introducing uncertainty in their expected levels at subsequent time points. Moreover, we hypothesize that cells in proximity of each other at one time point tend to follow similar trajectories and thus remain close over time - a property not guaranteed by standard cell-wise OT. To overcome these limitations, we developed a representation that captures the continuous nature of the cellular state space while remaining robust to feature fluctuations. Since cells form continuous distributions rather than discrete clusters, we model this landscape as a mixture of Gaussian distributions, each represented by a distinct low-dimensional approximation. We introduce a Hierarchical-Feature Expectation-Maximization (HF-EM) approach, designed to define cellular states across time in a way that supports consistent temporal mapping, independent of a cell state's dynamic events. In this framework, we distinguish dynamic features – those fluctuating faster than the measurement timestep, such as cell cycle and signaling proteins – from more stable features that evolve more gradually over time. A cell's probability of belonging to each Gaussian in the mixture is determined solely by stable features, while dynamic features are used for parameter refinement. This formulation yields a mean vector capturing the stable, overarching characteristics of each cell state, along with latent factors that represent within component variability driven by dynamic processes. This representation captures both the identity of each cell state and its associated activity programs, providing insights into its functional response. By representing cellular states in this hierarchical manner, our approach enables more accurate inference of state transitions over time using OT. We first illustrate the challenges of temporally mapping features with different dynamics, including cell cycle activity, using both simulated and experimental data, and then show the improvements achieved with our methodology. Finally, we are applying HF-EM to a 4i timeseries dataset from Pelkmans lab, including both signaling and cell cycle activities, to show the utility of HF-EM for dissecting cellular responses by inferring state transition trajectories upon drug perturbation.

Modelling cell-cell interactions with random graphs

Mike van Santvoort[1], Yiyan Wu[2], Joan Kant[2], Federico Gaiti[2], Pim van der Hoorn[1#], Federica Eduati[1#]

[1]Eindhoven University of Technology, The Netherlands; [2]Princess Margaret Cancer Centre, University of Toronto, Canada

[#]shared last authorship

The tumor microenvironment (TME) is a complex molecular ecosystem whose overall state cannot be explained by examining interactions between cells in isolation. To understand how it drives cancer development, it must therefore be modeled as an integrated system. With the rise of different technologies that profile the TME (e.g. bulk RNA-sequencing and spatial omics), it is increasingly important to create modelling frameworks that are both interpretable and adaptable to new data types. We will present a flexible mathematical framework able to generate patient-specific instances of the TME by sampling random networks consistent with diverse input data modalities. The model comes in two varieties: RaCInG – a published model that uses predominantly bulk RNA-seq data as input[1] – and SpaCInG – a new extension designed for spatial omics data. Both are connected to inhomogeneous random digraphs[2] and compute the probability that two cells of given types communicate with each other, while also attributing the contribution of individual ligand–receptor pairs to these interactions. From these probabilities more complex network features can also be derived analytically thanks to the model's mathematical foundation. An example of such feature is the relative size of the largest strongly connected component in the network, which reflects the level of influence the tumor has on its microenvironment. If for a feature no mathematical proof exists, both models also have a Monte-Carlo formulation through which features can be extracted numerically and their stability tested. We will present our modelling framework and apply it to two types of TME input data: bulk RNA-seq data, and spatial omics data. Using bulk RNA-seq data from TCGA solid tumors, RaCInG classifies TME subtypes and predicts levels of immune infiltration. In two independent cohorts with known response to immunotherapy, RaCInG further predicts patient response and highlights the molecular drivers underlying non-response. In the spatial omics application we focus on glioblastoma to explore what additional insights can be gained with SpaCInG. We will show that SpaCInG can find interactions which are indicative of the location the sample is taken from (tumor core or edge), as well as infer the directionality of protein signaling within them. SpaCInG recapitulates known ligand-receptor interactions between malignant core cells and macrophages, revealing how their crosstalk promotes an immunosuppressive, pro-tumor microenvironment characterized by angiogenesis and tissue-repair responses. At the tumor edge, SpaCInG uncovers interactions between malignant cells and neurons, including the formation of neuron-tumor synapses, engagement of NOTCH signaling, and the establishment of a neurotrophic niche. All in all, this framework highlights the value of RaCInG and SpaCInG as both practical tools for modelling the TME and rigorous mathematical models deserving of theoretical consideration.

1. van Santvoort M, Lapuente-Santana Ó, Zopoglou M, et al. Mathematically mapping the network of cells in the tumor microenvironment. *Cell Rep Methods*. 2025;5(2):100985. doi:10.1016/j.crmeth.2025.100985
2. van Santvoort M, van der Hoorn P. From inhomogeneous random digraphs to random graphs with fixed arc counts. arXiv:2309.06066. doi:10.48550/arXiv.2309.06066. Submitted.

Simulation-Driven Representation Learning for Cell Motility Data

Kumaran Bala Kandan Viswanathan, Inge Wortel, Tom Claassen

Radboud University, Nijmegen, The Netherlands

Introduction: Movement is a key property of immune cells, and a better understanding of their motion helps both our fundamental understanding of the immune system and can contribute to applications like immunotherapy. Recent advances in representation learning have proven powerful for scientific discovery in several biological disciplines, for example by revealing previously unrecognised biological patterns from intricate genomic datasets.[1] Despite these advancements, representation learning remains challenging in the domain of immune cell motion videos, largely because the limited availability of publicly available and annotated immune cell motion data makes it hard to train and evaluate models in this domain. In this work, we build on a benchmark annotated dataset of two-photon immune cell motion videos from the Cell Behaviour Classification challenge (CBVCC), consisting of 300 video instances with labelled motion patterns.[2] As this valuable dataset is still too small to train and test robust representation learning, we extend it using established computational models that simulate realistic cell motion, while preserving complexities present in the CBVCC dataset. Importantly, these simulations enable us to generate unlimited data with high-quality ground truth without relying on manual annotations. We show how this simulated dataset can be used to test and improve representation learning methods. Method: We employ an extended cellular potts model to simulate time-lapse datasets modelled after the CBVCC, in which cells exhibit either linear or defined turning behaviours that can be explicitly imposed on the simulated cell. To learn representations from simulated data, we use a group-convolutional neural network (G-CNN) optimised using the contrastive learning loss.[3] This method can learn generalizable representations because it is invariant to rotational variations present in the data. We then use our simulated dataset to systematically assess to what extent the (known) interventions are covered by the learned representation. Results: In this work, we generated 5000 simulated videos modelled after the CBVCC and found that rich representations can be captured with a dataset size of 3200 video instances. We show that we can tailor these models to reflect the complex cell-motion dynamical aspects of the CBVCC data, such as cellular heterogeneity, deformation, background noise, and the simultaneous presence of multiple cells within the field of view. As a proof of concept, we assess how these feature attributes impact the capacity of the representation learning method to capture and interpret meaningful representations of cell motion. We find that particularly artefacts and other cells in the background increase the risk of overfitting on irrelevant features, especially on small datasets. To mitigate such overfitting, our work provides a systematic approach to estimate how much data is needed. Furthermore, the simulation framework enables the incremental introduction of complexity, allowing for a comprehensive evaluation of the robustness of learned representations to data artefacts. Discussion: Our work demonstrates that the simulated dataset provides a robust and comprehensive baseline for evaluating representation methods applied to cell motion video data. Furthermore, it shows under which conditions the features learned through representation learning are meaningful and generalizable to new datasets. In future work, this simulation framework could be leveraged to identify the limitations of current methods and thereby facilitate the development of more robust representation learning techniques for cell motion video datasets.

References:

1. Yun T, Cosentino J, Behsaz B, et al. Unsupervised representation learning on high-dimensional clinical data improves genomic discovery and prediction. *Nat Genet*. 2024;56(8):1604-1613. doi:10.1038/s41588-024-01831-6
2. Cabini RF, Barkauskas D, Chen G. Cell Behavior Video Classification Challenge, a benchmark for computer vision methods in live-cell imaging. Research Square. 2025. doi:10.21203/rs.3.rs-6667194/v1
3. Wang T, Isola P. Understanding contrastive representation learning through alignment and uniformity on the hypersphere. *In Proceedings of the 37th International Conference on Machine Learning (ICML'20).* 2020;119(921):9929–9939. doi:10.5555/3524938.3525859

Reconstructing Stem-Cell Population Dynamics from Somatic-Mutation Phylogenies in Ageing Mice

Lea Weber

Deutsches Krebsforschungszentrum (DKFZ), Heidelberg, Germany

Somatic mutations accumulate steadily throughout life in long-lived stem and progenitor cells and serve as natural lineage markers. In haematopoiesis, single-cell sequencing of such variants enables the reconstruction of phylogenetic trees that capture historical relationships among haematopoietic stem and progenitor cells (HSPCs). These trees encode information about past proliferation, differentiation and clonal persistence, yet extracting dynamical properties from their structure requires a rigorous mathematical framework. Here, using murine single-cell somatic variant data from young and aged mice, we develop methods to infer HSPC population dynamics from phylogenetic tree topology, branch-length distributions and clade-size asymmetries. Our approach addresses two questions. First, we test whether the observed murine trees are compatible with neutral evolutionary models -- models in which clones expand by chance alone, without selective advantage -- by comparing empirical tree statistics to predictions from classical neutral branching processes. Second, we investigate deviations from neutrality, asking whether observed patterns in aged mice can be explained by altered proliferation rates, differentiation biases or changes in compartmental structure. Complementing the stem cell phylogenies, additional single-cell data from downstream progenitor cells hints at the presence of distinct HSC subpopulations, including cells that preferentially commit to direct megakaryocyte production. These observations suggest that heterogeneity in stem-cell types may contribute to non-neutral clonal dynamics and influence lineage output in ageing haematopoiesis. Our results demonstrate that mathematical analysis of somatic-variant phylogenies provides a powerful framework for inferring hidden aspects of stem-cell population dynamics. This approach offers a general strategy for testing neutrality, quantifying lineage biases and linking tree geometry to dynamical constraints in hierarchically organised somatic tissues.

Spatiotemporal modeling of signaling pathways: impact of endosomal compartmentalization and application to gonadotropin receptors

Chloé Weckel[1,2]*, Romain Yvinec[1,2]*, Stefan Haar[2#], Frédéric Jean-Alphonse[1,2#]

[1]BIOS, PRC, UMR CNRS, Université de Tours, Centre INRAE Val de Loire, Nouzilly, France; [2]MUSCA, Université Paris-Saclay, Inria Centre Saclay–Île-de-France, Palaiseau, France

*shared first authorship; #shared last authorship

Cells communicate with each other by sending extra-cellular ligands such as hormones. Once recognized by their receptors at the plasma membrane, those ligands trigger a signaling cascade within the cell. It is now widely recognized that G Protein-Coupled Receptors (GPCR) are able to trigger signaling cascades both at the plasma membrane and, once internalized, from different endosomal compartments. Furthermore, signal kinetics and spatial localization are major determinants of the cellular response to a given stimulus. Receptor trafficking (internalization/recycling/endosomal dynamics) is therefore a key process in signaling pathways, yet often overlooked in theoretical GPCR dynamic models. In the first part of our study, we developed a new mathematical framework to incorporate receptor trafficking and signal compartmentalization into generic GPCR models. Using a compartmentalized model based on systems of ordinary differential equations (Chemical Reaction Networks), we studied the effects of internalization and recycling on receptor-induced cellular responses. This approach helped us to address two reciprocal questions: (i) How does trafficking influence cellular responses? and (ii) Does cellular response affect trafficking? For the first case, we demonstrated that receptor trafficking can either enhance or reduce pharmacological action of ligands, depending on plasma membrane versus endosomal signaling properties. For the second case, we reveal that signal feedback on receptor trafficking can induce complex phenomena like multi-stability. In the second part of our study, we applied this theoretical framework to the Follicle-Stimulating Hormone Receptor (FSHR) signaling pathway. By calibrating our model with high-throughput kinetic data by using pyPESTO and Petab, we show how accounting for receptor trafficking improves pharmacological characterization of ligands and advances our understanding of FSHR signaling pathways.

Cooperative motility emerges in crowds of T cells but not neutrophils

Inge Wortel[1,2]*, Jérémy Postat[3,4]*, Mihaela Mihaylova[1], Mauricio Merino[3,4], Aanya Bhagrath[3,4], Maryl Harris[3,4], Lin Wouters[1], Lucas Wiebke[5], Daniel Parisi[5], Judith Mandl[3,4,6#], Johannes Textor[1,2#]

[1]Data Science, Institute for Computing and Information Sciences, Radboud University, Nijmegen, The Netherlands; [2]Medical BioSciences, Radboudumc, Nijmegen, The Netherlands; [3]McGill Research Centre for Complex Traits, McGill University, Montréal, QC, Canada; [4]Department of Physiology, McGill University, Montréal, QC, Canada; [5]Instituto Tecnológico de Buenos Aires (ITBA), C.A. de Buenos Aires, Argentina; [6]Department of Microbiology and Immunology, McGill University, Montréal, QC, Canada

*shared first authorship; #shared last authorship

MOTIVATION: T cells are among the most motile immune cells in the body, and their migration into and within tissues is key to their function. Remarkably, T cells can maintain their motility even in highly crowded environments like the densely packed T cell areas of lymphoid organs, but how they do so remains incompletely understood. A key challenge in answering this question is that crowd dynamics are the product of the T cell's individual movement, its interaction with the rest of the crowd, and environmental structures – and available data of crowded T cell motion in vivo does not allow us to untangle how each of these different factors contribute to the dynamics of the crowd. In this work, we address this challenge by taking inspiration from the broader field of crowding physics.[1] We focus on a hallmark scenario that has proven instrumental in characterizing other crowded systems such as pedestrians and ants: single-lane traffic. By letting T cells navigate the highly constrained but constant environment of single-lane microchannels both in vitro and in silico, we derive which cell-cell interactions are required to explain experimentally observed T-cell crowd dynamics. METHODS: To implement single-lane traffic for T cells in vitro, we fabricated microfluidic devices with straight channels (w x h = 6 x 5 μm) coated with fibronectin. T cells were isolated from mice expressing a reporter for filamentous actin (Lifeact-GFP) and a fluorescent protein localized to the nucleus (NLS-nTnG), activated with α-CD3/CD28 and exogenous IL-2, loaded into the devices for imaging, and tracked manually, yielding a dataset of 1481 tracks from 9 biological replicates. We also annotated which cells were in physical contact, allowing us to compare the dynamics of cells moving individually to those moving in groups. We similarly implemented several models of single-lane T-cell traffic in silico; a "minimal-interaction" model based on a previously published particle model for pedestrian dynamics,[2] and several variations of a cellular Potts model (CPM) of cell motility[3,4] in which we systematically varied cell-cell interaction mechanisms. RESULTS: We find that individual T cells move rapidly in narrow, straight microchannels, and are characterized by strong heterogeneity with cell speeds ranging from 5-30 um/min. These heterogeneous individuals nevertheless manage to form stable, motile "trains", with the speed of cell trains only 20% below that of single T cells. We find that this behavior hinges on cell interactions: minimal models in which cells only interact via physical exclusion consistently predict a much larger (~50%) speed drop in trains. Using a CPM model, we find two cell interaction mechanisms required to explain the formation of stable, motile trains: a preference of T cells to maintain contact with each other after collisions, and an ability of faster T cells to "push" slower ones (cooperation). Finally, we show that these mechanisms are cell type-specific: neutrophils in the same settings slow down with increasing cell density, with dynamics that are well-explained by minimal-interaction models. DISCUSSION: Our work reveals cell interaction mechanisms that allow for fluid motion despite high levels of crowding. In vivo, T cells encounter crowded tissue environments throughout their lifetime,[1] and cooperative motion may be key to preserve T cell motility in these conditions and prevent the "traffic jams" that impair motion in other crowded systems.

References:

1. Wortel IMN, Postat J, Mihaylova M, et al. Cooperative motility emerges in crowds of T cells but not neutrophils. bioRxiv. 2024. doi:10.1101/2024.10.21.618803
2. Baglietto G, Parisi DR. Continuous-space automaton model for pedestrian dynamics. *Phys. Rev. E.* 2011;83:056117. doi:10.1103/PhysRevE.83.056117

3. Niculescu I, Textor J, de Boer RJ. Crawling and Gliding: A Computational Model for Shape-Driven Cell Migration. *PLoS Comput Biol*. 2015;11(10):e1004280. doi:10.1371/journal.pcbi.1004280
4. Wortel IMN, Niculescu I, Kolijn PM, Gov NS, de Boer RJ, Textor J. Local actin dynamics couple speed and persistence in a cellular Potts model of cell migration. *Biophys J.* 2021;120(13):2609-2622. doi:10.1016/j.bpj.2021.04.036

Stochastic Evolution of Resistance in Acute Lymphoblastic Leukemia

Qianci Yang

Max Planck Institute for Evolutionary Biology, Plön, Germany

Acute lymphoblastic leukemia (ALL) is a type of cancer in which aberrant cells, such as lymphoblasts, accumulate in the bone marrow. Lymphoblasts are immature blood cells that arise during hematopoiesis. Uncontrolled proliferation of lymphoblasts, without further differentiation, leads to ALL. The primary treatment for most ALL cases is chemotherapy; however, after an intense treatment phase, relapse is observed in some patients. Early-stage relapses may be due to undetectable residual leukemia cells by conventional cytomorphology. Molecular tests for measurable residual disease (MRD) can quantify disease burden at relatively low levels, helping track cancer remission and relapse. We investigate the dynamics of residual disease in individual patients to mathematically model leukemia evolution and the resulting heterogeneity in observed response and relapse kinetics. From a bottom-up perspective, we developed stochastic and deterministic, patient-specific models that can integrate longitudinal MRD data to further the understanding of the driving factors of relapse. Conversely, from a top-down perspective, a machine learning approach was used to obtain the best-fit model structure and the most important features from the data. We found that pre-existing resistant subclone-driven relapse, de novo resistant subclone-driven relapse, and cancer plasticity caused relapse can be the underlying reason for some early relapses. The initial disease level reduction kinetics are important to predict the relapse. Our modelling provides a framework for using MRD kinetics to better quantify and predict relapse timing in individual patients, as well as to understand the main mechanisms that drive relapse. These insights are important for the development od digital twin representations of ALL.

Spatially resolving B cell clonal dynamics in human and murine tissues

Yang Zhao

Karolinska Institutet, Stockholm, Department of Medicine, Solna, Sweden

B cells are central players in adaptive immunity, performing diverse functions such as antibody production and antigen presentation. Each B cell expresses a unique, clonally inherited receptor (BCR) that can exist either as a membrane-bound receptor or as a secreted antibody, conferring antigen specificity. B cell activities are shaped by both their receptor repertoire and their spatial organization within tissues. Linking individual B cell clones to their native microenvironment is therefore essential to understand their functional roles. The in-house developed Spatial VDJ method enables mapping of B and T cell clonality within tissues, providing spatial information on B cell clonal dynamics. In our ongoing work, we are extending Spatial VDJ to preclinical models, including murine and macaque tissues, to investigate B cell clonal responses in tumors under immunotherapy and in vaccine studies, respectively. We are also further advancing the technology through co-capture of host–microbe interactions and adaptation to the high-resolution Visium HD platform. Together, Spatial VDJ can capture B cell clonal dynamics across species within with their microenvironments, with the potential to uncover how B cell clonality and spatial contexts influence immune responses in health, disease, and vaccination settings.

Organoid cell fate dynamics in space and time

Xuan Zheng

Hubrecht Institute, Utrecht, The Netherlands

Organoids are a major new tool to study tissue renewal. However, characterizing the underlying differentiation dynamics remains challenging. Here, we developed TypeTracker, which identifies cell fates by AI-enabled cell tracking and propagating end point fates back along the branched lineage trees. Cells that ultimately migrate to the villus commit to their new type early, when still deep inside the crypt, with important consequences: (i) Secretory cells commit before terminal division, with secretory fates emerging symmetrically in sister cells. (ii) Different secretory types descend from distinct stem cell lineages rather than an omnipotent secretory progenitor. (iii) The ratio between secretory and absorptive cells is strongly affected by proliferation after commitment. (iv) Spatial patterning occurs after commitment through type-dependent cell rearrangements. This “commit-then-sort” model contrasts with the conventional conveyor belt picture, where cells differentiate by moving up the crypt-villus axis and hence raises new questions about the underlying commitment and sorting mechanisms.

A semi-continuous Graph-ODE approach with flow-based formulations to avoid quadratic system growth in Lagrangian metapopulation models

Henrik Zunker

German Aerospace Center (DLR), Cologne, Germany

Estimating commuter movements and mobility is essential to inform spatial epidemic dynamics. Explicit Lagrangian metapopulation models based on ordinary differential equations (ODEs) typically track one ODE state vector per commuter group. However, this results in near-quadratic growth of the overall system with respect to the number of spatial patches. We introduce a flow-based model formulation that integrates only patch totals and determines commuter updates by proportional rescaling of integrated flows. On any interval without mobility events and under homogeneous mixing, we prove an equivalence between the explicit commuter-compartment ODEs and our flow formulation. Numerically, we provide two realization options. A direct left-share update rescales integrated total flows once per step. A Runge Kutta stage-aligned update evaluates commuter derivatives at the same stages as a (single step) Runge Kutta solver of the total system and inherits its order.

In our numerical experiments, the direct left-share update shows the expected first-order error profile. The stage-aligned variant matches the explicit model to solver accuracy. Benchmarks up to 1024 patches and six age groups show near-linear scaling for the flow-based variants and speedups up to four orders of magnitude over the explicit scheme at large network sizes. The reformulation also offers instant access to integrated transition counts, such as daily new infections, which simplifies calibration and reporting.

Optimal Theory in Surveillance and Intervention Strategies for African Swine Fever and Highly Pathogenic Avian Influenza

Alfredo Acosta[1], Clara Delecroix[2], Timothée Vergne[2], Jana Schulz[1]

[1]Friedrich-Loeffler-Institut, Institute of Epidemiology, Greifswald, Germany; [2]IHAP, Université de Toulouse, INRAE, ENVT, Toulouse, France

Introduction: Optimal control theory is applied in daily domains where multi-objective decision making is essential, such as logistics (delivery optimisation), navigation (route planning), or monetary policy design. It can enhance surveillance and intervention strategies by systematically exploring a wide range of possibilities. The choice of an optimal strategy is highly dependent on the objective, which may target specific epidemic features, such as a minimizing epidemic duration or detecting cases as early as possible, while also accounting for the costs of both the epidemic and the interventions. Using a series of case studies, we aim to develop an optimisation pipeline for surveillance and intervention strategies for high-priority animal infectious diseases in the Wiliman-ID EU project context. Materials and Methods: To test different objective functions, we first applied optimization frameworks identified through a comprehensive literature review. Mechanistic epidemic models for African Swine Fever (ASF) in Germany and Highly Pathogenic Avian Influenza (HPAI) in France were implemented in R, integrating a cost function considering the epidemic features to evaluate the strategies. The function combined direct intervention cost with estimated impact of cases. We applied a global-local hybrid optimization algorithm, and explored a range of unit cost and constraints to identify optimal combinations of strategies and to assess how adjustments affected the objective functions. Results Preliminary optimisation results enabled the identification of intervention strategies that balanced different intervention measures. Choosing a relevant objective function is crucial as results varied, depending on epidemic features across the tested grid of unit costs. Several key patterns emerged: - Trade-offs for HPAI: higher vaccination costs shifted the optimal strategy toward increased culling proportions, while lower culling costs favoured broader vaccination coverage. - Optimal Ratios for ASF: The ratio between two strategies varied across scenarios, and allowed to identify the optimal combination between carcass removal and hunting pressure. Discussion and Conclusions A well-defined objective function allows for a transparent evaluation of interventions under varying epidemiological and economic conditions. Including the costs in animal epidemic models ensures that strategies are realistic and feasible, aligning with economic constraints while enhancing intervention effectiveness.

Dissecting CD8+ T cell dynamic responses in adoptive T-cell transfer therapy of melanoma

Nissrin Alachkar, Maike Effern, Michael Hölzel, Kevin Thurley

Institute for Experimental Oncology, University Hospital Bonn, Germany

$CD8^+$ T cells are central to anti-tumour immunity, directly targeting and eliminating cancer cells. Under constant antigen stimulation, however, they progressively lose effector function through exhaustion, ultimately compromising tumour control. The differentiation trajectory of $CD8^+$ T cells, particularly transitions between effector, stem-like progenitor exhausted, progenitor exhausted, and terminally exhausted states, critically shapes the immune response. To investigate these processes, we performed a high-dimensional longitudinal flow cytometry experiment of adoptive T cell therapy (ACT) in a murine melanoma model.[1] The dataset comprises distinct $CD8^+$ T cell subsets sampled from blood, spleen, brachial and tumour-draining lymph nodes, and tumour tissue at multiple time points post-ACT. Using unsupervised high-dimensional clustering, we identify and quantify $CD8^+$ T cell subsets across organs and time, enabling us to track their kinetics during tumour progression. We then employ our data-driven modelling framework that incorporates response-time distributions to capture intracellular processes.[2] Within this framework, we construct a set of candidate mathematical models representing alternative $CD8^+$ T cell differentiation pathways, each defined by distinct lineage relationships. We fit these models to the experimental data and use model-selection criteria to identify the differentiation motif that best explains the observed dynamics. Overall, we present a systematic inference of $CD8^+$ T cell differentiation pathways, providing mechanistic insight into how these subsets shape anti-tumour responses.

References

1. Effern M, Glodde N, Braun M, et al. Adoptive T Cell Therapy Targeting Different Gene Products Reveals Diverse and Context-Dependent Immune Evasion in Melanoma. *Immunity*. 2020;53(3):564-580.e9. doi:10.1016/j.immuni.2020.07.007
2. Burt P, Thurley K. Distribution modeling quantifies collective T_H cell decision circuits in chronic inflammation. *Sci Adv*. 2023;9(37):eadg7668. doi:10.1126/sciadv.adg766

A Deep Learning Framework for Multi-Site Signal Peptide Cleavage Prediction

Carolina Alvarez Garavito[1,2], Marc Vaisband[1,2], Annika Frauenstein[3,4], Benedikt Gansen[3], André C. Michaelis[4], Andreas U. Lindner[3], Lea Nguyen[3], Jose J. Almagro Armenteros[5], Matthias Mann[4], Søren Brunak[5], Felix Meissner[3,4], Jan Hasenauer[1,2]

[1]Life & Medical Sciences (LIMES) Institute, University of Bonn, Germany; [2]Bonn Center for Mathematical Life Sciences, University of Bonn, Germany; [3]Institute of Innate Immunity, Department of Systems Immunology and Proteomics, Medical Faculty, University of Bonn, Germany; [4]Max Planck Institute of Biochemistry, Martinsried, Germany; [5]Novo Nordisk Foundation Center for Protein Research, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark

Signal peptide cleavage site (CS) prediction is a key step in understanding protein maturation, yet existing tools such as the state-of-the-art SignalP 6.0 (SP6) are limited to identifying a single most likely cleavage site. Many proteins, however, exhibit multiple biologically relevant N-terminal processing events. Motivated by a novel experimentally validated compendium of neo-N-termini, we developed a deep learning model that predicts multiple CS candidates by leveraging embeddings from two protein language models, ProtBERT and ESM-2, together with a conditional random field (CRF) decoder. Our approach replaces single-path Viterbi decoding with CRF marginal probabilities, yielding a full probability distribution over all amino acids in the sequence and thus enabling principled ranking of plausible CSs. To compare fairly with SP6 in a multi-site setting, we implemented SP6-Rank, a variant of SP6 that also uses marginal probabilities rather than Viterbi decoding. Our results show that the proposed model outperforms SP6-Rank in recovering secondary cleavage sites across proteins with multiple N-terminal processing events. In addition, we outline a probabilistic strategy for inferring whether a protein is likely to harbor more than one CS based on the structure of the marginal distribution, providing an interpretable indicator of multi-site maturation. This probabilistic framework offers a mathematically grounded approach to multiple CS prediction and supports the study of proteins with a spectrum of different N-termini.

scGNNPred: Explainable graph neural networks for scRNA-seq-based phenotype classification

Shubhi Ambast, Karola Mai, Charles Mwangi Kaumbutha, Matthias Becker

Modular High-Performance Computing and Artificial Intelligence, German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany

Single-cell RNA sequencing has enabled high-resolution characterization of cellular heterogeneity, offering valuable insights into disease mechanisms. However, translating single-cell data into patient-level prediction remains challenging due to the complexity, sample variability, and limited cohort sizes. To address these limitations, we propose scGNNPred, a novel graph neural network (GNN)-based framework for classifying disease states from scRNA-seq data. Our approach models each patient's scRNA-seq expression data as a graph, where nodes represent individual cells, node features capture gene expression profiles, and edges reflect cell-cell similarity. By leveraging the representational power of GNNs, our approach learns interactions between cells and captures key biological patterns underlying disease phenotypes. To address the challenge of varying cell counts and heterogeneous cell populations across patients, we employ hierarchical pooling techniques that retain the most informative cellular substructures and preserve essential topological features. To further enhance predictive performance and stabilize embeddings, we explore supervised contrastive learning. We evaluated scGNNPred across multiple datasets, including chronic kidney disease (CKD), idiopathic pulmonary fibrosis (IPF), Alzheimer's disease (PBMCs), and COVID-19 (PBMCs). The framework achieved strong classification performance, particularly in CKD and IPF datasets, where epithelial and fibroblast populations were highly informative. For PBMC datasets, immune subsets including proliferating monocytes were identified as critical contributors, highlighting disease-relevant biology. Interpretability analyses using cell- and gene-level importance scores, mapped back to the original data, revealed patterns consistent with known literature for each disease. Our results demonstrate the potential of GNNs to bridge the gap between cell-level data from scRNA-seq and patient-level insights.

Simulation-Based Inference of Cell Migration Dynamics in Complex Spatial Environments

Jonas Arruda[1], Emad Alamoudi[1], Robert Mueller[2], Marc Vaisband[1], Ronja Molkenbur[1], Jack Merrin[3], Eva Kiermaier[4], Jan Hasenauer[1]

[1]University of Bonn, Germany; [2]TUD Dresden University of Technology, Germany; [3]Institute of Science and Technology Austria, Austria; [4]Friedrich-Alexander University Erlangen-Nürnberg, Germany

To assess cell migration in complex spatial environments, microfabricated chips, such as mazes and pillar forests, are routinely used to impose spatial and mechanical constraints, and cell trajectories are followed within these structures by advanced imaging techniques. In systems mechanobiology, computational models serve as essential tools to uncover how physical geometry influences intracellular dynamics; however, decoding such complex behaviors requires advanced inference techniques. Here, we integrated experimental observations of dendritic cell migration in a geometrically constrained microenvironment into a Cellular Potts model. We demonstrated that these spatial constraints modulate the motility dynamics, including speed and directional changes. We show that classical summary statistics, such as mean squared displacement and turning angle distributions, can resolve key mechanistic features but fail to extract richer spatiotemporal patterns, limiting accurate parameter inference. To solve this, we applied neural posterior estimation with in-the-loop learning of summary features. This learned summary representation of the data enables robust and flexible parameter inference, providing a data-driven framework for model calibration and advancing quantitative analysis of cell migration in structured microenvironments.

Robust Global Model Analysis via the Stochastic Profile Likelihood Approximation

Rafael Arutjunjan, Jens Timmer

Institute of Physics, University of Freiburg, Germany

The profile likelihood method constitutes the gold standard in establishing accurate confidence intervals for non-linear models with many parameters. However, this is far from its only use. At a glance, it reveals the structural and practical non-identifiability of individual parameters by determining for which parameters the profile likelihood is exactly flat and which confidence intervals are unbounded in one or both directions. While this already highlights potential targets for model reduction, even more nuanced information can be extracted. By inspecting how the nuisance parameters change along a particular profile, it can be quantified how strongly parameters are coupled, providing key insights into how model mechanisms influence each other and combine to drive the overall system behaviour. The main drawback of the profile likelihood approach derives from its considerable computational cost, since it requires the re-optimisation of all nuisance parameters at every step along a profile. As a result, calculating profile likelihoods at multiple stages during the model development process is not always feasible for particularly complex models due to time constraints and limited computational resources. To address this issue, we introduce the Stochastic Profile Likelihood Approximation (SPLA) and demonstrate how it can be used to investigate models in direct analogy to its namesake. At its core, the approximation consists of sampling the log-likelihood over the entire parameter space, discretising the individual parameter ranges into bins and finally determining the best log-likelihood value observed during sampling, for which the parameter of interest was inside a given bin. The stochastic nature of this approach provides flexible control over the trade-off between the quality of the approximation and computational cost. Therefore, in many cases the same insights as offered by the conventional profile likelihood can be gained at a fraction of the computational burden. Furthermore, our method does not require the location of the global optimum to be known beforehand, thus making it ideally suited for rapid iterative development of model candidates and allowing the more resource-intensive calculation of the exact profile likelihood to be postponed until the final stage of the modelling process. We also illustrate the robustness of the SPLA against some of the issues which can arise during numerical computations of the conventional profile likelihood in practice. The compelling simplicity of our proposed method allows it to be implemented into modelling frameworks which compute the likelihood via relatively few additional lines of code and thus easily integrated into existing workflows.

Beyond mechanistic modeling: bridging the gap from signaling to phenotypical readout

Severin Bang, Jens Timmer

Institute of Physics, University Freiburg, Germany; CIBSS Centre for Integrative Biological Signalling Studies Freiburg, Germany; Freiburg Center for Data Analysis and Modeling, Freiburg, Germany

Mechanistic modeling of intracellular signal transduction is a well-established and successful technique that provides valuable insights into biological processes, particularly in the context of cancer research. While mechanistic modeling is a highly informative approach for studying the biochemical differences between healthy and cancerous cells, its application is constrained to biochemical processes for which a mechanistic description is feasible. This poses a significant limitation, particularly when attempting to expand the scope of interest from the signaling itself to encompass the resulting phenotypic reaction e.g. the proliferative response. Conventional methodologies generally entail the compartmentalization of signaling from the proliferative response, employing the former as an input for a linear model of the latter. We propose an alternative approach that utilizes a surrogate non-mechanistic model to construct an integrated model of signaling and the phenotypic response. This approach offers the advantage of greatly expanding the scope of the model while circumventing sources of error and loss of information that are characteristic of the typical split approach.

Graph-Based Modeling of Spatial Organization in Developing and Tumor Tissues

Florian Bartsch[1,2], Miriam Wandres[1,3], Svea Beier[1,3], Anastasiya Boltengagen[1], Angelika Eggert[2,4], Nikolaus Rajewsky[1,3,5,6,7,8,9]

[1]Laboratory for Systems Biology of Regulatory Elements, Berlin Institute for Medical Systems Biology (BIMSB), Max-Delbrück-Centrum for Molecular Medicine in the Helmholtz Association (MDC), Berlin, Germany; [2]Department of Pediatric Oncology and Hematology, Charité - Universitätsmedizin Berlin, Berlin, Germany; [3]Humboldt-University of Berlin, Berlin, Germany; [4]Universitätsklinikum Essen, Essen, Germany; [5]Charité - Universitätsmedizin Berlin, Berlin, Germany; [6]German Center for Cardiovascular Research (DZHK), Berlin, Germany; [7]NeuroCure Cluster of Excellence, Berlin, Germany; [8]German Cancer Consortium (DKTK), Heidelberg, Germany; [9]National Center for Tumor Diseases (NCT), Berlin, Germany

Tissue microenvironments are dynamic systems of diverse, interacting cell types whose spatial organization is crucial for tumor heterogeneity. Spatial architecture shape tumorigenesis, and therapeutic response. Understanding the molecular mechanisms that drive these spatiotemporal interactions is key for predicting and controlling disease trajectories. By leveraging our in-house developed, high-resolution and high-throughput Spatial Transcriptomics (ST) technique (Open-ST, Schott et al. Cell 2024), we identify spatial patterns within and across datasets at single-cell resolution. However, even though these datasets are extremely information-rich, they remain static molecular snapshots that do not directly capture temporal gene regulation. Here we report on our progress in developing a computational framework derived from Graph Convolutional Networks (GCNs) trained on spatially informed cell-cell neighborhood graphs for reconstruction and prediction of latent features. By exploiting latent space embeddings, we aim to explain tissue remodeling by mapping model predictions to molecular mechanism. We apply this approach to developing human brain organoids across five timepoints. Preliminary results show that the model captures spatially varying gene activation patterns and latent relationships, whereas principal components of activations directly capture latent variables. This data-driven strategy aims to unravel mechanisms within and across ST datasets. We will extend this analysis to a heterogenous cohort of pediatric tumors (neuroblastoma) from cancer patients to systematically characterize spatial organization and heterogeneity in high- and low-risk tumors.

Model-Based Design for Morphogen-Driven Spatial Patterns in Synthetic Biology

Amatus Beyer

University of Stuttgart, ISA, MMSCS, Germany

The evolution of multicellular organisms from single cells represents a remarkable triumph of cooperation and communication in the life sciences. To achieve this, cells need the capacity to adhere to one another, engage in communication, and orchestrate gene expression in a manner that facilitates specialization and proper positioning within the organism. Morphogenesis, defined as the process by which cells coordinate to form defined shapes, is central to the development of multicellular organisms. The objective of synthetic developmental biology is to emulate these processes through the design of orthogonal genetic circuits that produce predictable cellular patterns and shapes. Intercellular communication, frequently facilitated by morphogens (diffusing signaling molecules) during development, plays a pivotal role in guiding cellular behavior within tissues. In accordance with our vision of model-based design of defined synthetic multicellular arrangements, we extended a synthetic Notch morphogen circuit model, established by Toda et al., by incorporating morphogen-dependent proliferation.[1,2] This extended model provides a framework for the exploration of how variations in the size and location of morphogen sources, interactions with cells and morphogen inhibitors influence cellular behavior and tissue organization. Our modeling framework supports the design of cellular circuits and their arrangement, with the aim of predicting optimal configurations for desired tissue architectures. This serves as a foundation for further advancements inspired by the work of Mousavi and Lobo, who proposed the automatic design of gene regulatory mechanisms for spatial pattern formation using two orthogonal static morphogen gradients.[3] By integrating these elements, our approach aligns with the broader goal of advancing synthetic developmental biology towards the creation of intricate multicellular systems. Beyond elucidating fundamental principles in morphogenesis, this bottom-up engineering approach opens new avenues for designing complex tissues with specific functions and applications in regenerative medicine. The potential to create intricate and functional multicellular architectures not only contributes to developmental biology but also to therapeutic strategies that harness the body's own capacity for regeneration.

References

1. Toda S, McKeithan WL, Hakkinen TJ, Lopez P, Klein OD, Lim WA. Engineering synthetic morphogen systems that can program multicellular patterning. *Science*. 2020;370(6514):327-331. doi:10.1126/science.abc0033
2. Beyer A, Wagner V, Klingerl V, Heymann M, Radde N. Extending a synthetic Notch morphogen circuit model to construct 2D cell structures. *IFAC-PapersOnLine*. 2024;58(23):31–36. doi:10.1016/j.ifacol.2024.10.006
3. Mousavi R, Konuru SH, Lobo D. Inference of dynamic spatial GRN models with multi-GPU evolutionary computation. *Brief Bioinform*. 2021;22(5):bbab104. doi:10.1093/bib/bbab104

Immune competence alters neurodevelopmental vulnerability to micro- and nanoplastic exposure in human brain organoids

Nelli Blank-Stein[1], Marina Mayer[1], Omkar Suhas Vinchure[2], Maria Francesca Viola[1], Marie Schott[3], Nikolaus Rajewsky[3], Jay Gopalakrishnan[2], Elvira Mass[1]

[1]Developmental Biology of the Immune System, Life and Medical Sciences Institute, University of Bonn, Germany; [2]Institute of Human Genetics, University Hospital, Friedrich Schiller University Jena, Germany; [3]Laboratory for Systems Biology of Regulatory Elements, Berlin Institute for Medical Systems Biology (BIMSB), Max-Delbrück-Centrum for Molecular Medicine in the Helmholtz Association (MDC), Berlin, Germany

Brain development is shaped by tightly regulated genetic programs and environmental influences. Micro- and nanoplastics (MNPs) are increasingly detected in human tissues, yet their impact on neurodevelopment remains poorly defined. Here, we investigated the consequences of MNP exposure using complementary human iPSC-derived brain organoid systems with and without integrated microglia. During early developmental stages in high throughput brain organoids, chronic MNP exposure resulted in reduced organoid growth, altered ventricular zone (VZ) architecture, and diminished progenitor density. At more

advanced stages, single-nucleus RNA sequencing revealed disrupted neurodevelopmental trajectories characterized by reduced neuronal maturation, altered radial glia signatures, and increased stress-associated neuronal populations. In immune-competent cerebral organoids, MNP exposure was associated with altered proliferative activity during early development. Differences in overall organoid growth became apparent at later developmental stages, with reduced size observed in microglia-free organoids. Notably, organoids containing microglia were largely protected from this growth reduction. At advanced stages, spatial transcriptomic analyses revealed context-dependent alterations in metabolic pathway activity, including changes in cholesterol-related and mitochondrial energy metabolism signatures in MNP exposed organoids containing microglia compared to matched microglia-containing organoids without MNP exposure. Consistent with these transcriptional patterns, lipidomic profiling demonstrated remodeling of lipid composition at advanced stages, whereas no significant lipid alterations were observed during earlier stages. To further assess microglial responses, induced microglial-like cells (iMGLs) were acutely exposed to MNPs for short-term stimulation. While particle uptake did not induce classical inflammatory responses, transcriptomic and protein-level analyses revealed metabolic reprogramming characterized by reduced glucose metabolism and increased fatty acid biosynthesis. Collectively, these findings indicate stage dependent neurodevelopmental and metabolic alterations following MNP exposure and suggest that microglia modulate organoid responses to plastic particles.

A comparison of three methods for estimating the probability of a major outbreak

Karla Bonic-Babic, Philip Maini, Robin Thompson

University of Oxford, UK

Background & Aims: Early in an infectious disease outbreak, it is often unclear whether the pathogen will fade out or escalate into a major epidemic. Accurate estimation of the probability of a major outbreak (PMO) from early disease incidence data can support public health decision-making by providing an assessment of the threat posed by the invading pathogen. In this study, we compare three methods for estimating the PMO based on early case counts: i) Method 1: an analytic approach based on branching process theory; ii) Method 2: a simulation-based trajectory matching method; and iii) Method 3: a machine learning classifier trained on simulated data. Methods & Results: We assume that outbreak dynamics are governed by a stochastic renewal equation model with an unknown reproduction number (with a specified prior). Under Method 1, we use Bayesian inference to estimate the reproduction number and calculate the PMO analytically using standard branching process theory. Under Method 2, we select the subset of outbreaks (from a simulated training dataset) that exactly match the early outbreak trajectory and calculate the proportion of those that result in an outbreak with more than 100 cases in total. Under Method 3, we use the same training dataset to train a random forest classifier to predict, from the early outbreak trajectory, the probability that the outbreak will develop into one in which more than 100 cases occur. All three methods produce consistent PMO estimates. We investigate the number of training simulations required to obtain accurate estimates under Methods 2 and 3, and find that the required number varies depending on whether the ongoing outbreak represents a common or rare occurrence in the training dataset. We find that Method 1 provides an approach for calculating the PMO quickly and accurately (for the assumed renewal equation model), and can easily be adjusted to explore counterfactual scenarios involving different future control interventions. On the other hand, Methods 2 and 3 are more easily extensible than Method 1 for use with more complex epidemiological models, since they simply require repeated model simulation, but require additional computational resources to run. We further extend the framework to incorporate underreporting, using a Bayesian approach that links observed case counts to true infection counts via a reporting probability and integrates over both transmission and observation uncertainty. Across all methods, underreporting leads all methods to underestimate the true probability of a major outbreak, especially for low-incidence sequences; however, the methods respond to this effect in a consistent manner. Implications: This work provides a rigorous comparison of three methods for estimating the PMO from early outbreak data. This research identifies scenarios in which analytic methods are appropriate and those in which simulation-based or machine learning-based methods can complement classic analytic approaches. We hope that this work will enable accurate outbreak risk assessments to be generated quickly in future infectious disease outbreaks.

Improved Autism Spectrum Disorder Detection using Machine Learning Methods: An Integration of fMRI and RNA Seq Data

Reindorf Borkor[1], Chipo Zidana[2], Michelle Carey[3]

[1]Kwame Nkrumah University of Science and Technology, Kumasi, Ghana; [2]Botswana International University of Science and Technology, Botswana; [3]University College Dublin, Ireland

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition influenced by both genetic and neurological factors. The disease is associated with stigma due to its effects on the neurological functions of the brain. It is therefore important to identify the major brain regions of interest (ROI) associated with autism, together with their corresponding functions to assess the neurological impacts on the structure and functions of the brain for individuals with autism. This study seeks to employ an integrated approach to investigate the neurological effects of autism on children between 7-12 years through the integration of Magnetic Resonance Imaging (MRI) and gene expression (RNA-Seq) data using the ABIDE data sets. By identifying genes that responsible for ASD in children using genetic data, these were then used to identify then ROI associated with ASD neuroimage features from the MRI scans. The neuroimage features identified through genomic association are the used as a variable selection criterion to enhance the ASD classification and understand its underlying biological and physical features associated with ASD. Advanced machine learning models, including Random Forest, Lasso Logistic Regression, and neural networks, were applied to classify ASD presence based on multimodal features. The findings reveal significant genetic variations associated with altered brain structures, particularly in the prefrontal cortex, cerebellum, and corpus callosum, regions linked to ASD-related cognitive and behavioural traits. This study demonstrates the potential of combining neuroimaging and genomics for improved ASD diagnosis and a deeper understanding of its neurobiological basis.

Spectral radius–based analytical evaluation of how daily contact rate fluctuations influence infectious disease dynamics

Aleksandr Bryzgalov[1], Tyll Krueger[2]

[1]Martin Luther University Halle-Wittenberg, Germany; [2]Wroclaw University of Science and Technology, Poland

The dynamics of daily contact rates can play a key role in the spread of infectious diseases. Several studies have shown that contact rates vary throughout the week — for example, they decrease at workplaces and schools during weekends, but increase among active population groups (ages 18–35) on Fridays and Saturdays.[1,2] Noticeable fluctuations also occur during working days. However, such variations are often averaged out in analyses and models to simplify the process. Under certain conditions — involving specific combinations of infectious period, latent period, and infectivity per contact — ignoring daily contact variations can lead to inaccurate estimates of the basic reproduction number. We present an analytical method that enables fast and accurate assessment of the impact of daily contact rate variations on infection spread. We define the type of an infected individual as the weekday on which they got infected. The initial spread of an epidemic starting with a few infected individuals is then given by a multi-type Poisson branching process, which can be specified by a 7x7 matrix of the expected number of secondary type j cases generated by an infected type i individual. The spectral radius of this matrix corresponds to the basic reproduction number R_0. We show furthermore that the relative prevalence P of such an epidemic in the limit of large populations is given by the largest solution of $\mathrm{P} = 1 - \exp(-\mathrm{P} \cdot \mathrm{R}_0)$. The approach can be extended to the continuous time case where one has a potential continuum of types. The basic reproduction number is then given by the spectral radius of the transfer operator associated with the corresponding multi-type branching process. The prevalence is given again by the largest solution of the above equation. We also discuss the generalization to several population groups (for example, working and non-working populations). The SIR model with weekday heterogeneity of contact structure is also an example for a larger class of problems where epidemiologically relevant types of individuals are not a priori given but are dynamically generated. Contrary SIR epidemic process on heterogeneous contact structures for which a good asymptotic theory exists, how to estimate the prevalence of this question remains open for dynamically generated heterogeneity. The problem is closely related to the difficulty of defining a proper backward branching process for the epidemics. We present results for several combinations of infectious period, latent period, and transmission probability per contact, as well as for different patterns of daily contact variations. For comparison, we also provide results based on averaged daily contact rates and on simulations from an individual-based model. Noticeable differences are observed between scenarios using averaged versus exact daily contact rates, which could determine whether the system remains below or exceeds the epidemic threshold. The proposed analytical approach provides a precise assessment of the impact of contact rate variations on infection spread in a highly mixed population. The method offers a solid theoretical basis for calibrating and validating various model types (both compartmental and individual-based). Furthermore, it helps build intuition about how specific changes in daily contact rates affect infection dynamics. This method combines the advantages of fast computation with improved accuracy compared to classical SEIR models.

1. Mossong J, Hens N, Jit M, et al. Social contacts and mixing patterns relevant to the spread of infectious diseases. *PLoS Med*. 2008;5(3):e74. doi:10.1371/journal.pmed.0050074
2. Phuong HT, Bartz A, Jarynowski AK, et al. Changes in social contact patterns in Germany during the SARS-CoV-2 pandemic - an analysis based on the COVIMOD study. *BMC Infect Dis.* 2025;25(1):588. doi:10.1186/s12879-025-10917-3
3. Bollobás, B. Random Graphs. 2nd ed. Cambridge University Press. 2001

Bridging Model and Data: A Parametrization-and-Projection Method for Overdetermined Stochastic Inverse Problems in Systems Biology

Benjamin Castellaz*, Timo Glöckle*, Nicole Radde

Institute for Stochastics and Application, University of Stuttgart, Germany

*shared first authorship

Advances in computational power, alongside improved software libraries and greater standardization, have led to an unprecedented adoption of complex predictive modelling approaches in systems biology. Simultaneously, advances in measurement technologies have enabled the collection of increasingly complex datasets. These data often display substantial variability that cannot be fully attributed to measurement noise, indicating that intrinsic variability in the underlying biological systems must be considered. Consequently, calibrating computational models to explain this type of data remains challenging. We interpret the calibration problem as a Stochastic Inverse Problem (SIP), where the observations are interpreted as samples from a random variable. The solution of the SIP is a parameter distribution that reproduces the distribution of the observations when pushed forward through the model. We argue that in many cases this approach better represents the actual experimental setup than typical Bayesian approaches. A particular challenge in SIPs are overdetermined problems, where the observations do not necessarily lie in the range of the model. We propose a novel method to find solutions to overdetermined SIPs that minimize the mismatch to the data in a sample-wise least-squares sense. To achieve this, we first approximate the model's image manifold using a surrogate model and then project the observations orthogonally onto this manifold. Using this approach, we explain German district-specific COVID-19 infection data through an ordinary differential equation model. Our calibrated model accurately predicts unseen data, validating the approach. Supported by a solid mathematical foundation and an easy-to-use Python package, our framework provides a flexible approach for integrating observational data into simulation models in the overdetermined setting, enabling broad applicability across research domains.

Replacing Markovian Assumptions with Non-Markovian Reality in Epidemic Parameter Estimation

Sunhwa Choi

Innovation Center for Industrial Mathematics, National Institute for Mathematical Sciences, Seongnam, Republic of Korea

Epidemic models traditionally assume that everyone progresses through infection stages at a constant, memoryless rate, but real diseases do not behave this way—people who have been exposed longer are more likely to become infectious, and infectious periods rarely follow simple exponential patterns. Because of this mismatch, widely used methods systematically overestimate key parameters such as the reproduction number and even misidentify the initial epidemic state. In this talk, I introduce two data-driven, history-dependent frameworks that fix these problems. The first incorporates realistic gamma-shaped latent and infectious periods, enabling accurate reproduction-number estimation directly from confirmed-case data. The second reconstructs hidden exposure histories to accurately infer the initial number of exposed individuals, even under noisy or rapidly changing outbreak conditions. Together, these approaches replace decades-old assumptions with realistic disease dynamics, removing major sources of bias and yielding more trustworthy epidemic predictions.

References

- Hong H, Eom E, Lee H, Choi S, Choi B, Kim JK. Overcoming bias in estimating epidemiological parameters with realistic history-dependent disease spread dynamics. *Nat Commun.* 2024;15(1):8734. doi:10.1038/s41467-024-53095-7
- Lim D, Ko KT, Hong H, et al. A history-dependent approach for accurate initial condition estimation in epidemic models. *PLoS Comput Biol*. 2025;21(9):e1013438. doi:10.1371/journal.pcbi.101343

Poster No. 17: Infectious Disease Modelling

Use of a Scattered Light Integrating Collector (SLIC) for Point of Care Testing to detect bacteria in fluid samples from Prosthetic Joint Infections of the lower limb

Isabelle Cochrane[1,2], Phil Walmsley[2], Rob Hammond[2], Frank Schildberg[1]

[1]University of Bonn, Germany; [2]University of St Andrews, UK

Introduction: Prosthetic Joint Infection (PJI) complicates 1% of lower limb arthroplasty cases, conferring high morbidity and mortality. Early targeted antibiotic therapy represents good antimicrobial stewardship, and improves patient outcomes, but our ability to deliver this is limited by the current 72 hour turnaround for confirming infection and antimicrobial susceptibilities. We propose a novel diagnostic technology, the Scattered Light Integrating Collector (SLIC), a label-free method of bacterial detection, whose sensitivity permits bacterial growth tracking in real time. SLIC shines a 600nm laser at a suspension of infected material; organisms scatter the light, which is collected in an integrating sphere, and directed towards a photodiode, which in turn produces a signal This can be visualised as a growth curve. Previous work on blood cultures and urine suggests SLIC detects infection in <30 minutes and delineates antimicrobial sensitivities in <2 hours. We investigate whether SLIC can be translated to the diagnosis of PJI. We aim to improve the robustness of our methods of detection and susceptibility testing in the face of the heterogeneous surgical samples, with the goal to inform antibiotic choice within an intraoperative timeframe. Methods: Serial dilutions of laboratory strain *S. aureus* and *E. coli* were tested in SLIC over 24 hours, to characterise their growth curves. Subsequently, laboratory strains of six organisms common in PJI were tested against six antibiotics at consecutive doubling dilutions, to establish antimicrobial susceptibilities in each of the resulting 36 test combinations.A dedicated R script was written to parse and graphically represent SLIC outputs, and to extricate growth metrics:Time to detection (TTD) of infection was defined as the time at which the growth trace exceeded background noise. This was calculated as the mean + 2x standard deviations of the first two minutes of the trace (pre-growth baseline).Growth curve characteristics, including growth rate (derivative), percapita derivative, lag time, Area Under the Curve (AUC) and maximum density were extracted using a model-free approach, utilising the gcplyr package in R. The endpoint growth density (EP) was also logged.The standard definition of > 90% growth suppression on overnight Broth Microdilution (BMD) was used as a benchmark for determining antimicrobial susceptibility in each test combination. AUC and EP analyses were performed on the SLIC trace for each test combination, and these derived measurements were expressed as a percentage of the positive control trace, to quantify growth suppression and derive susceptibilities. Results: SLIC produces reproducible growth curves for each organism, with a recognizable lag and log phase. Lag time and time to positivity are negatively correlated with starting concentration (Spearman rho = -0.985, -0.989 respectively, p<0.001), but independent of antibiotic dosing. AUC decreases with falling starting concentration (rho = -0.985, p <0.001), and changes linearly with lag time (Pearson r = -0.97, p<0.001). Maximum growth is independent of starting concentration. Antibiotics produce dose-dependent growth suppression by AUC and EP peak (rho = -0.75, -0.73 respectively, p <0.001). TTD was <20 minutes for all organisms when seeded at 105 cfu/ml.AUC methodology achieved 77% agreement at 2h against BMD, with EP achieving 80%. EP showed better diagnostic accuracy than AUC analysis, with high positive predictive values for resistance (80-87.5% at 1h, 88.2-92.3% at 2h). AUC analysis gave fewer Very Major Errors (range 2.7-13.8% depending on timing, vs 11.1-22.2% for EP); EP gave the fewest Major Errors (2.8-11.1% vs 8-36% for AUC). Conclusion: SLIC is an excellent tool for predicting resistance to antimicrobial agents as early as 60 minutes, comparing favourably to current laboratory standards. This establishes SLIC as a rapid, accurate method for informing early antimicrobial therapy in PJI.

Optimal control and cost-effectiveness analysis of a two-strain bacterial meningitis epidemic model: Insights for effective public health interventions

Monica Veronica Crankson[1], Afez Abidemi[2]

[1]University of Mines and Technology, Tarkwa, Ghana; [2]Department of Mathematical Sciences, Federal University of Technology, Akure, Ondo State, Nigeria

Bacterial meningitis remains a critical public health concern, particularly in sub-Saharan Africa and countries within the meningitis belt, where recurrent outbreaks result in significant morbidity and long-term disabilities among survivors. Despite advancements in treatment, the disease continues to pose a major threat due to its rapid transmission and debilitating effects. This study presents an optimal control model for the transmission dynamics of bacterial meningitis, focusing on a two-strain scenario that more accurately reflects real-world conditions. The model incorporates strategies such as effective human personal protection, vaccination for both strains and treatment for timely and de- layed diagnosis to assess their impact on disease control, with an emphasis on minimizing long-term consequences for the recovered population. Using Pontryagin's Maximum Principle (PMP), we establish the existence of its solution and char- acterize the controls. The Forward-Backward Sweep (FBS) method is employed to solve the optimal control problem, including the adjoint equations, for better numerical solutions. Real-life data from the Ghana Center for Disease Control is utilized to parameterize the model, ensuring its relevance to endemic regions. The results reveal that the most efficient and cost-effective strategy involves the combined use of all five control variables. In particular, a strategy involving the human personal protection (such as face masks) also emerges as a highly effective approach. Based on these findings, we provide action- able recommendations for policymakers in endemic areas, emphasizing cost-efficient interventions that can significantly reduce the burden of bacterial meningitis.

Deciphering the effect of (R)-2-hydroxyglutarate (2-HG) on the tumor microenvironment of IDH mutant gliomas

Sina Dadmand[1], Minh Deo[1], Julian Taranda[1], Sevin Turcan[2]

[1]Clinical Cooperation Unit Neurooncology (B320), German Cancer Research Center (DKFZ), Heidelberg, Germany; [2]Department of Neurooncology, Center for Neurology, University Hospital Bonn, Germany

Mutations in isocitrate dehydrogenase 1 (IDH1) define lower grade gliomas and result in the accumulation of the oncometabolite 2-hydroxyglutarate (2-HG), which disrupts cellular epigenetics, differentiation, and immune responses. However, how 2-HG alters the glioma tumor microenvironment (TME), particularly at the level of immune and stromal programming, remains poorly understood. To investigate this, we used patient-derived IDH1-R132H–mutant oligodendroglioma cells and implanted them orthotopically into immunodeficient mice. In parallel, we included a sham group that underwent the same surgical procedure without tumor injection, representing non–tumor-bearing nude mouse brains. We then profiled the brain TME under three conditions,sham, tumor-bearing + vehicle, and tumor-bearing + IDH inhibitor, vorasidenib, using single-cell RNA sequencing and spatial transcriptomics. Treatment with vorasidenib caused significant reprogramming of the TME. Homeostatic microglia expanded, while $CCR2^{+}$ infiltrating macrophages and plasmacytoid dendritic cells decreased. Transcriptional activity in immune cells was broadly suppressed, including downregulation of STAT1, REL, MYC, IRF1/5/7/9, STAT2, and the inflammatory kinase CDK8. Cell–cell interaction inference (LIANA) revealed a weakening of inflammatory chemokine signaling, particularly CCL2/4/12–CCR1/2/5, while homeostasis-associated interactions (e.g., PTN–PTPRS, PSAP–LRP1) were retained. Beyond immune populations, mouse oligodendrocyte and OPC populations also shifted transcriptionally. These cells downregulated programs associated with proliferation (e.g., MYC/E2F, mTOR/OxPhos) and showed increased expression of neuronal-interaction and differentiation-related states. Spatial transcriptomics confirmed the presence of infiltrating mouse macrophages within human tumor regions and revealed structured spatial segregation between the tumor core, tumor–brain interface, and normal brain. Together, our findings demonstrate that suppression of 2-HG with mutant IDH1 inhibition attenuates inflammation, remodels intercellular communication, and promotes homeostatic and differentiated states in the glioma-associated microenvironment. These insights underscore the role of metabolic reprogramming in modulating glioma–host interactions.

Learning Density-Dependent Cell-Cycle Regulation with UDEs

Luke De Bretton-Gordon

Mathematics Institute, The University of Oxford, UK

We extend the density-dependent model of cell cycle progression (Falcó et al., 2024) by replacing the prior-assumed linear transition rates with positivity- and monotonicity-constrained neural networks, within a Universal Differential Equation (UDE) framework. This hybrid approach preserves mechanistic structure – including diffusive cell motion and mass balance between cell-cycle compartments – while allowing real experimental data of expanding epithelial monolayers to determine the functional shape of transition rates. The learned rates reveal qualitative features not accessible under the original linear crowding assumptions: (i) a nonzero baseline rate for the transition even at high densities, consistent with the biological expectation that cells committed to division must complete mitosis, and (ii) inhibition thresholds below which the transition rates remain at their maximal values. We assess robustness via synthetic-data recovery and bootstrap ensembles, finding these qualitative features stable across credible bands.

JANUS: Joint ANalysis for augmentation of clUSter specificity

Talip Yasir Demirtas, Maximilian Billmann

Institute of Human Genetics, University of Bonn, School of Medicine & University Hospital Bonn, Bonn, Germany

Background/ Objective CRISPR screens systematically identify genes that impact various specific biological processes. To gain specificity of a screening experiment, the effect of a gene perturbation on a specific phenotype or the differential effect on cell fitness in a process-sensitizing context is measured. However, hit lists from these experiments typically include genes that have specific effects on the process as well as pleiotropic genes, which impact the process indirectly or directly. Here, we develop an algorithm JANUS (Joint ANalysis for augmentation of clUSter specificity) that leverages public large CRISPR screening resources (The Cancer Dependency Map) to structure hit lists of phenotypes specific CRISPR screens and assign specificity and pleiotropy scores to each cluster. Methods JANUS jointly analyzes the screening set of interest and a selected reference data set such as the DepMap by quantifying how much the screening set of interest contributes to each gene cluster. Variance contributed by individual screens is quantified through partial correlation analysis. We used global and process-specific precision-recall analyses with gold standards to quantify functional information of gene-pairs and clusters. Results We apply JANUS to a set of 7 genome-wide CRISPR screens that investigate mitochondrial drug-gene interactions of energy metabolism. We show that JANUS increases the specificity and resolution of mitochondrial clusters. We applied JANUS to tissue-specific clustering, demonstrating that tissue-specific clusters connect both lowly mutated genes and cancer genes. Conclusion JANUS will help analyze and interpret complex phenotypic CRISPR screens by utilizing the rapidly growing number of simple fitness screens to systematically address the genotype-to-phenotype problem.

Efficient Integration of Binary Qualitative Data into ODE Model Estimation

Domagoj Doresic, Daniel Weindl, Jan Hasenauer

Bonn Center for Mathematical Life Sciences, University of Bonn, Germany; Life and Medical Sciences (LIMES) Institute, University of Bonn, Germany

Ordinary differential equation (ODE) models are typically calibrated using quantitative measurements, which are often limited in scope and lead to wide predictive uncertainties. In contrast, binary qualitative readouts, such as gene essentiality, cell survival/death, or presence/absence of phenotypes, are abundantly available but challenging to integrate probabilistically into parameter estimation frameworks. We present a likelihood-based approach for efficiently incorporating binary qualitative data into ODE model calibration. Our method employs a logistic link function on monotone model features (e.g., cell viability ratios) to predict the probability of binary outcomes, enabling gradient-based hierarchical parameter estimation. The likelihood-based formulation naturally supports uncertainty quantification and structural identifiability analysis, providing a statistical foundation for parameter inference. We apply our method to a large-scale cancer cell line model encompassing ERBB, RAS, and PI3K-AKT signaling pathways (1,228 species, 4,104 parameters). While the model was originally calibrated using ~16,000 CellTiter-Glo viability measurements, we extend the calibration by integrating 1,926 binary gene essentiality observations from CRISPR screens across 107 genes and 18 cell lines. Our results demonstrate that binary data integration improves model predictions. We provide a systematic comparison with ordinal data methods to characterize the computational efficiency and statistical properties of different approaches for integrating qualitative information. The proposed method offers a tailored and scalable framework for binary data that is both computationally efficient and statistically rigorous, enabling broader use of qualitative measurements in mechanistic modeling.

Simulation of ultra-high dose rate (UHDR) irradiations using a Monte Carlo-based dose engine

Janne Frenz[1]*, Celine Karle[1,2]*, Thomas Tessonnier[3,4], Amir Abdollahi[1,3,5,6,7,8], Andrea Mairani[1,3,7,9]

[1]Clinical Cooperation Unit Translational Radiation Oncology, National Center for Tumor Diseases (NCT), Heidelberg University Hospital (UKHD) and German Cancer Research Center (DKFZ), Heidelberg, Germany; [2]Department of Physics and Astronomy, Heidelberg University, Heidelberg, Germany; [3]Heidelberg Ion-Beam Therapy Center (HIT), Department of Radiation Oncology, Heidelberg University Hospital (UKHD), Heidelberg, Germany; [4]Clinical Cooperation Unit Radiation Oncology, National Center for Tumor Diseases (NCT), German Cancer Research Center (DKFZ), Heidelberg, Germany; [5]German Cancer Consortium (DKTK) Core-Center Heidelberg, German Cancer Research Center (DKFZ), Heidelberg, Germany; [6]Division of Molecular and Translational Radiation Oncology, Department of Radiation Oncology, Heidelberg Faculty of Medicine (MFHD), Heidelberg; [7]Heidelberg Institute of Radiation Oncology (HIRO), Heidelberg Faculty of Medicine (MFHD), Heidelberg, Germany; [8]National Center for Radiation Oncology (NCRO), Heidelberg Institute of Radiation Oncology, Heidelberg University and German Cancer Research Center (DKFZ), Heidelberg, Germany; [9]National Center for Oncological Hadrontherapy (CNAO), Medical Physics, Pavia, Italy

*shared first authorship

The main challenge of radiation therapy (RT) is delivering a dose sufficiently high to kill tumor cells, while simultaneously minimizing the damage to surrounding organs. This is especially difficult when an organ-at-risk (OAR) lies close to the tumor. There are many ways to address these conflicting goals. In intensity-modulated radiation therapy (IMRT), the field is modulated to fit the patient's anatomy. This can be achieved by steering a small beam across predefined spots on the target. Each of these spots can be irradiated with a different dose. Additionally, using multiple beams from different directions ensures a highly conformal tumor coverage. IMRT requires solving an inverse planning problem. For OARs and regions of interest (ROIs), a spot pattern is generated. Then the scan spot weights are optimized based on a cost function which measures the agreement between dose goals and current dose distribution. In the simplest case, the dose function d is the product of the vector of scan spot weights $\mathrm{x} \in \mathrm{R}^{\mathrm{n}}$ with the dose influence matrix (DIM) D. The DIM is an $\mathrm{m} \times \mathrm{n}$ matrix, where $\mathrm{m}, \mathrm{n} \in \mathrm{N}$ are the number of voxels in the target and the number of scan spots, respectively. Entry $\mathrm{d}_{\mathrm{i,j}}$ contains the dose contribution of beam j to voxel i in Gy/particle. The DIM is generated using an analytical or a Monte Carlo- (MC) based dose engine. The optimization problem is expressed in a cost function $\mathrm{C(x)} \coloneqq \sum_{\mathrm{i=1}}^{\mathrm{n}} \mathrm{w_i}\, \mathrm{C_i(x)}$, where the $(\mathrm{w_i})_{\mathrm{i}} \geq 0$ are weights and $\mathrm{x} \geq 0$ is subject to constraints $\mathrm{g_k(x)} \leq 0,\ 1 \leq \mathrm{k} \leq \mathrm{M}$. Each term $\mathrm{C_i}$ penalizes the deviation from the goals in a fixed field. Minimizing the cost function compromises between the possibly conflicting dose goals of ROIs and OARs. Lately, the paradigm of maximal dose to the tumor, minimal dose to healthy tissue, has been extended. The FLASH effect describes the in vivo phenomenon of cells tolerating high doses better when delivered at ultra-high dose rates (UHDR, > 40 Gy/s). However, which dose rate (DR) parameter best models the effect is controversial. Candidates comprise mean DR (total dose/total irradiation time), d5-95 DR (consider the time between 5 and 95 % of total dose delivery), and instantaneous DRs. Investigating UHDR irradiation is difficult. There is no agreement on uniform experimental endpoints, and the setups differ widely. A remedy can be in silico experiments. In our work, we aim to extend our in-house MC dose engine, MonteRay (MR), by including dose rate optimization. Given a beam plan and the target's geometry, we use MR to generate a DIM. To ensure the quality of this preliminary dose data, we compared DIMs with corresponding forward calculations. In the next step, we compute a dose rate profile with a resolution of 50 μs for each voxel from the DIM, beam plan, and (possibly hypothetical) spill file. Since the question of which dose rate parameter is decisive in FLASH modelling remains unclear, we extensively validated the simulated dose rates against measurements, considering all three DR measures mentioned above. Additionally, we investigated the reproducibility of irradiations at our beam line with regard to factors crucial for the simulation. The measurements in question were carbon irradiations performed on different field sizes, scanning patterns, and days. A diamond detector in a water tank measured the dose in the irradiated field at a resolution of 50 μs. The final step will be to include dose rates as a parameter in MR's optimization process, possibly by performing dose rate computations in MR and adding a term to the cost function. In this manner, we will be able to optimize plans for existing and

hypothetical beam lines. We hope this will enable in silico experiments to help investigate the FLASH effect and standardize research efforts.

Modelling the impact of autoimmune hepetatis on liver cirrhosis progression

Ransford Ganyo

University of Cape Coast, Ghana

Autoimmune Hepatitis (AIH) is a chronic inflammatory liver disease in which the immune system attacks the liver cells, leading to inflammation and cirrhosis if left untreated. It constitutes a determinant etiologic factor in the genesis of liver cirrhosis. In spite of its importance, most mathematical models focused on the effect of alcohol consumption and hepatitis B infection (HBI) in liver cirrhosis progression have overlooked AIH. In this paper, we incorporate autoimmune hepatitis into an SICR (Susceptible-Infective-Cirrhotic-Recovered) model and investigate its effect on the dynamics of liver cirrhosis progress, accounting for both hepatitis B infection and heavy drinking among individuals. The model shows theoretical soundness and biological significance that all solutions are positive and bounded. The disease-free equilibrium (DFE) was asymptotically stable if $\mathrm{R}_{01} < \mathrm{R}_{02} < 1$ and the endemic equilibrium (EE), asymptotically stable if $\mathrm{R}_{02} > \mathrm{R}_{01} > 1$. Mathematical simulations indicate that autoimmune hepatitis increases liver cirrhosis by 9\% and 56\% for minimum and maximum alcohol intake, respectively. These results imply that alcohol suppresses the immune system and consequently mitigates the impact of autoimmune hepatitis on liver cirrhosis but may have long-term adverse effects due to its pro-inflammatory properties.

Data-driven multi-scale modeling of the tumor micro-environment using interpretable machine learning

Suman Gare[1], Antonio de Jesus Ortiz Gonzalez[2,3], Lukas Kiwitz[1], Gemma van der Voort[4], Joanna Schnorr[1], Michelle Yong[4], Michael Hölzel[4], Marieta Toma[5], Jan Hasenauer[2,3], Alexander Effland[3,6], Kevin Thurley[1,3]

[1]Institute of Experimental Oncology, Biomathematics Division, University Hospital Bonn, Bonn, Germany; [2]Life and Medical Sciences (LIMES) Institute, University of Bonn, Bonn, Germany; [3]Bonn Center for Mathematical Life Sciences, University of Bonn, Bonn, Germany; [4]Institute of Experimental Oncology, University Hospital Bonn, Bonn, Germany; [5]Institute of Pathology, University Hospital Bonn, Medical Faculty, University of Bonn, Bonn, Germany; [6]Institute of Applied Mathematics, University of Bonn, Bonn, Germany

The tumor microenvironment (TME) is a key determinant of cancer progression and therapeutic response. Deciphering its spatial organization and cellular interactions is essential for identifying prognostic biomarkers and understanding immune regulation. Recent advances in multiplexed imaging and machine learning (ML) enable high-dimensional characterization of tissue architecture, yet integrating spatial and clinical data into interpretable, predictive models remains a challenge. We present a multi-modal, multi-scale ML framework that integrates spatially resolved CODEX imaging data with clinical variables to predict survival outcomes in cholangiocarcinoma, an aggressive malignancy with a median survival of 18–24 months. The framework, developed and validated using patient-derived CODEX tissue microarrays and clinical records from University Hospital Bonn, employs modality-specific feature encoders with orthogonality constraints to disentangle latent representations, a gating-based attention mechanism to adaptively weight modalities, and a low-rank Kronecker fusion module for integrative prediction. Combining spatial imaging with clinical features substantially improved survival prediction and enabled interpretable insights into the prognostic architecture of the TME. Image analysis pipelines, facilitated robust cell segmentation, phenotyping, and quantification of spatial organization patterns critical for model training. In parallel, we developed a spatio-temporal reaction–diffusion modeling framework using agent-based simulations in Morpheus to mechanistically study cytokine-mediated immune cell communication within the TME. The model captures secretion, diffusion, and uptake of cytokines, and represents intracellular signaling through phosphorylated STAT5 dynamics. Simulations reveal how cytokine gradients and cell motility jointly shape spatially heterogeneous signaling patterns, offering mechanistic context to the image-derived observations. Together, these computational approaches bridge data-driven inference and mechanistic understanding. By linking quantitative spatial imaging, clinical outcomes, and mathematical modeling, this work outlines a path toward data-based, testable models of tumor–immune interactions. Such integrative frameworks hold promise for identifying actionable biomarkers and guiding therapeutic strategies to enhance anti-tumor immunity.

Modeling spatially heterogeneous infectious disease spread with chances and challenges

Carlotta Felicia Gerstein[1,2], Martin Joachim Kühn[1,2,3]

[1]Life & Medical Sciences Institute (LIMES), University of Bonn, Bonn, Germany; [2]Bonn Center for Mathematical Life Sciences, University of Bonn, Bonn, Germany; [3]Institute of Software Technology, Department of High-Performance Computing, German Aerospace Center, Cologne, Germany

Infectious diseases will always emerge from individual transmission events. Without counteraction, strong or loose coupling between different regions will then lead to a broader or even global disease spread, generally showing spatially heterogeneous dynamics. Mathematical models integrating spatial resolution are powerful tools for studying adequate intervention strategies in advance. Among these models are different types of metapopulation models working on an aggregated subpopulation basis or agent-based models explicitly modeling individual features and decisions. However, with increasingly fine resolution, many challenges arise through the system size and number of parameters to be derived or estimated. In order to correctly address these issues, efficient and scalable methods are needed. In this presentation, we will discuss different scalable methods available with the MEmilio software framework which have recently been applied to several use cases from Sars-CoV-2 and Influenza.

Neural Stem Cells Reroute Metabolism Under SHH Stress in Parkinson's

Mohammadamin Ghasemi[1], Kevin Thurley[2], Rudi Balling[1]

[1]Institute of Molecular Psychiatry, University of Bonn, Germany; [2]Institute of Experimental Oncology, University Hospital Bonn, Germany

Neural stem cells (NSCs) are key players in brain homeostasis and regeneration, and their dysfunction may represent one of the earliest events in neurodegenerative diseases like Parkinson's. Prior work on reprogrammed patient-derived cells identified a SHH-driven NSC state (NSC2a) marked by impaired mitochondrial function — specifically a bottleneck at α-ketoglutarate dehydrogenase — but the downstream metabolic consequences remained unclear. In this study, we reanalyzed the same transcriptomic dataset using a pseudo-bulk approach to uncover subtle, cell type–specific signals. While pathway enrichment initially pointed toward cell cycle activation, deeper examination of differentially expressed genes in NSC2a revealed a striking upregulation of genes involved in cholesterol biosynthesis (ACAT2, RNF145), fatty acid metabolism (HACD3, DDHD1), and redox regulation (SLC25A10). Importantly, GSEA confirmed that the full cholesterol biosynthesis pathway was enriched — even though most individual genes weren't strong DEGs — suggesting a coordinated shift in lipid metabolism. Proteomic data from the same cohort independently supported this finding, showing elevated fatty acid and TCA cycle activity. Together, the data suggest that NSC2a cells reroute acetyl-CoA away from energy production and toward lipid remodeling, perhaps as an adaptive response to SHH-induced stress. Interestingly, this metabolic signature echoes findings in Alzheimer's disease models, where disrupted lipid metabolism in NSCs impairs their proliferation and fate decisions. Our results highlight a potential SHH–lipid axis in early disease states, revealing how metabolic rewiring may shape NSC vulnerability — and possibly neurodegenerative progression — long before neuronal loss becomes apparent.

Mathematical Modeling of EMT Pathways in Cancer Invasion Through PDEs

Nakshatra Ghosh

University of Bonn, Germany

Invasion- the process of the entry of the tumour cells inside the tissue domain by degrading the extracellular matrix(ECM), along with metastasis has been considered to be the cause of almost 90 % cancer related deaths. Cancer cells can be primarily distinguished into two main types- the epithelial like cancer cells and the mesenchymal like cancer cells. The basis of this differentiation is primarily due to their invasiveness or their proliferative capacity. This dilemma in cancer cells is extensively called the go-or-grow dichotomy, by which a cancer cell can either proliferate to the best of its abilities or continue migration at its peak, but not both. Among them, the mesenchymal cells have been considered more invasive, less proliferative phenotype where they can invade either as single cells or in clusters whereas the epithelial ones tend to invade less into the extracellular matrix, but proliferate at a higher rate. Thus, there exists a very critical role of the interplay between the two phenotypes through a process called epithelial-mesenchymal-transformation (EMT) and a reverse process called the called the mesenchymal-epithelial-transformation (MET) in the invasion-metastasis cascade. This paper investigates the use of partial differential equations(PDE)-based mod-elling approaches of the phenomenon of invasion involving the epithelial-mesenchymal-transformation (EMT) and mesenchymal-epithelial-transformation (MET). The set of PDEs involved the spatio-temporal dynamics of the epithelial phenotype, mesenchymal phenotype, diffusible matrix metalloprotease (MMP-2) and the extracellular matrix (ECM). A linear stability analysis was performed to confirm the eventual stability of the tumour free steady state and understand the travelling wave solutions of the model. Model parameters were also varied to generate results consistent with their biological interpretations. A genetic mutation of the more aggressive mesenchymal phenotype was also considered to show that it ameliorates the effective invasion rate of the cancer cells. ECM remodelling by fibroblasts is a common phenomenon in invasion to counterbalance the excessive degradation and on considering this additional assumption, it led the possible conclusion that EMT may be triggered by remodelling of ECM. Additionally the role of external cytokines like TGF-β or the reversal of the mesenchymal to the epithelial phenotypes was also modelled to understand their impact on the invasive dynamics. The final part of the paper deals with looking at trying different switch functions, and how considering additional factors like epithelial cell density for the switch functions could lead to a change in the invasion front of the cancer cells.

Keywords: Cancer invasion; Epithelial-Mesenchymal Transition (EMT); Mesenchymal-Epithelial Transition (MET); Go-or-Grow Dichotomy; Partial Differential Equations (PDE) Modelling; Extracellular Matrix (ECM); Matrix Metalloprotease (MMP); Tumour Dynamics; Linear Stability Analysis; Travelling Wave Solutions; Cytokines (TGF-β); Fibroblast-mediated ECM Remodelling.

Multicellular modelling of canonical NF-kB signaling

Sina Glöckner[1,2], Mareike Simon[1], Jana Wolf[1,2]

[1]Max Delbrück Center, Berlin, Germany; [2]Freie Universität Berlin, Germany

The NF-κB signaling system is a key mediator in the immune system and essential to the inflammatory response. After activation by diverse stimuli, such as cytokines or bacterial metabolical products, dimers of the NF-κB transcription factor family translocate to the nucleus and induce expression in a large set of target genes, including positive and negative regulators of the upstream pathway. In a single-cell context, NF-κB signaling has been extensively studied by experimental and computational methods. However, the immune response is a multicellular process; thus, multi-scale and multi-cell analyses are necessary to elucidate the effect of NF-κB signaling on cell-cell interactions. We approach this with a multi-scale, multi-cell modelling. To investigate the interaction between different cell types and stimuli, we extend the model to two NF-κB-expressing cell types in the intestinal crypt: sentinel macrophages and epithelial cells. There, the LPS-activated macrophages secrete TNFα to elicit an immune response in the epithel. By evaluating the resulting models in terms of sensitivity regarding signal transmission strength and speed as well as common single-cell measures, we can emphasize the importance of considering spatial and intercellular properties.

Evaluating the Performance of Parallel Optimization Methods for Large-Scale Dynamic Models in Computational Systems Biology

Stephan Grein[1,2], David R. Penas[3]

[1]Life and Medical Sciences (LIMES) Institute, University of Bonn, Bonn, Germany; [2]Bonn Center for Mathematical Life Sciences, University of Bonn, Bonn, Germany; [3]Computational Biology Lab, MBG-CSIC (Spanish National Research Council), Pontevedra, Spain

A central focus of systems biology is the effort to gain mechanistic insights by using dynamical models, which often are formulated using ordinary differential equations containing unknown parameters. By using the technique of parameter estimation, the parameters can be determined and models eventually be used to make predictions for the biological process of interest. In the case of large-scale dynamic models, these models often have many unknown parameters that need to be inferred from experimental data. This model calibration, also known as parameter estimation, is typically formulated as an optimization problem that seeks to identify the parameter values providing the best fit to the data. Yet, the inherent high dimensionality, multi-modal landscape, and non-linear, non-convex characteristics of the optimization domain render it computationally intensive and fraught with difficulties. To address these challenges, a wide array of optimization techniques has emerged, integrated into diverse software ecosystems and classified broadly into global or local strategies. Local approaches are typically subdivided into derivative-free and gradient-based variants, with some leveraging higher-order derivatives like Hessian approximations for enhanced convergence. Implementations vary across programming paradigms and, even within a single language, multiple algorithmic iterations exist, each imposing unique demands on computational resources and memory. Given the broad variety of optimization methods reported in the literature, this study aims to compare the efficiency of parallel optimization approaches, based on multi-start or cooperative strategies, using established efficiency and robustness metrics. The evaluation is conducted on a representative set of benchmark models from the PEtab collection, primarily drawn from published applications in systems biology. Furthermore, by using two high-performance computing infrastructures, we demonstrate the robustness and reproducibility of our findings. Ultimately, this research delivers an integrative appraisal of parallel optimization methodologies across a diverse array of models, equipping researchers with actionable insights into methodological trade-offs tailored to specific problem classes. By illuminating the relative merits and limitations of these methods, we empower the modeling community to adopt resilient, high-throughput strategies for parameter optimization in large-scale biological models.

Prediction of linear B cell epitopes using outlier detection and in-silico hydrolysis with protein language models

Jonas Guzik[1,2], Jörn Gethmann[1], Alexander Schulz[2], Barbara Hammer[2], Gereon Schares[1], Pavlo Maksimov[1], Hannes Bergmann[1]

[1]Friedrich-Loeffler-Institut, Federal Research Institute for Animal Health, Institute of Epidemiology, Greifswald-Insel Riems, Germany; [2]AG Machine Learning, Bielefeld University, Bielefeld, Germany

The accurate identification of linear B-cell epitopes is foundational for serological surveillance, vaccine development, immune profiling and the understanding of adaptive immune responses. Many computational methods for the prediction of linear B-cell epitopes from protein sequence have been developed, because experimental methods are costly and time-consuming. Available predictors are trained in a supervised manner, requiring both, defined epitopes and non-epitopes. However, defining a peptide as non-immunogenic is challenging from a biological perspective, as a peptide that is non-reactive in one biological context may still elicit an antibody response in another. Therefore, existing epitope predictors are hard to explain biologically and their ability to generalise beyond training data is limited. Here, we modelled linear B cell epitopes without dependence on a non-immunogenic peptide class by applying one-class classification and outlier detection methods to peptide embeddings from the largest available Evolutionary Scale Protein Language Model 2. For training, we used a large dataset of experimentally verified immunogenic peptides curated from the Immune Epitope Database. Whilst model training did not depend on non-immunogenic peptides, they were indeed required for tuning and evaluation. We developed a method referred to as ‘in-silico hydrolysis’, that generates reliable non-immunogenic peptide representations synthetically, by producing fragmented versions of the immunogenic training peptides. To evaluate the utility of these artificial non-epitopes, we used them to cross-validate our models and to train metric learning methods which we employed for dimensionality reduction before applying classic models for outlier detection. All our models and the existing BepiPred 3.0 method, a state-of-the-art predictor benchmark, were tested on peptide-array reactivity data from Toxoplasma gondii patient sera. All methods, including BepiPred 3.0, showed a performance that was close to random on the test data, which suggests that epitope predictions on antigen sequence alone are inherently limited. These findings indicate, that accurate B cell epitope prediction likely requires additional context information, such as antibody CDR sequences, to improve performance.

Learning Convex Temporal Regularizers for the Inverse Problem in ECGI

Manuel Haas[1], Thomas Grandits[2], Thomas Pinetz[3], Thomas Beiert[4], Simone Pezzuto[5], Alexander Effland[1]

[1]Institute for Applied Mathematics, University of Bonn, Germany; [2]Department of Mathematics and Scientific Computing, University of Graz, Austria; [3]Medical University Vienna, Austria; [4]Heart Center Bonn, Department of Internal Medicine II, University Hospital Bonn, Germany; [5]Department of Mathematics, University of Trento, Italy

Electrocardiographic imaging aims to non-invasively reconstruct cardiac electrical activity from sparse torso measurements, resulting in a severely ill-posed inverse problem. We introduce a finite element-based spatiotemporal regularization that combines total variation smoothing in space with a convex, learned Field of Experts-type prior in time. Reconstructions are computed via accelerated gradient descent by jointly minimizing a differentiable spatial term and the convex temporal regularizer. Neural network parameters are learned using deep equilibrium models with training sets of monodomain-simulated potentials. For white Gaussian noise perturbed observations, the proposed method outperforms standard handcrafted regularization techniques across multiple error metrics. The learned regularization effectively reduces temporal noise while preserving sharp transitions and accurately capturing cardiac dynamics.

Understanding CAR-T cell dynamics and therapeutic outcome for diffuse large B-cell lymphoma using mathematical modelling

Julia Hafenbrak[1], Viktoria Blumenberg[2,3,4], Simon Völkl[1,5,6], Veit Bücklein[2,3,4], Gerulf Hänel[2], Kai Rejeski[2,3,4], Louisa v. Baumgarten[7], Nathalie Albert[8], Fabian Müller[1,5,6], Andreas Mackensen[1,5,6], Marion Subklewe[2,3,4], Frederik Graw[1,5,6]

[1]Department of Internal Medicine 5, Haematology and Oncology, Friedrich-Alexander-Universität Erlangen-Nürnberg and Universitätsklinikum Erlangen, Erlangen, Germany; [2]Department of Medicine III, LMU University Hospital, LMU Munich, Munich, Germany; [3]Laboratory for Translational Cancer Immunology, LMU Gene Center, LMU Munich, Munich, Germany; [4]German Cancer Consortium (DKTK) and Bavarian Cancer Research Center (BZKF), partner site Munich, Munich, Germany; [5]Bavarian Cancer Research Centre (BZKF), Friedrich-Alexander-Universität Erlangen-Nürnberg and Universitätsklinikum Erlangen, Erlangen, Germany; [6]Deutsches Zentrum Immuntherapie (DZI), Friedrich-Alexander-Universität Erlangen-Nürnberg and Universitätsklinikum Erlangen, Erlangen, Germany; [7]Department of Neurosurgery, LMU University Hospital, LMU Munich, Munich, Germany; [8]Department of Nuclear Medicine, LMU University Hospital, LMU Munich, Munich, Germany

Genetically modified immune cells that are equipped with a chimeric-antigen receptor (CAR) to recognize cancer cells have shown remarkable success for the treatment of malignant diseases, such as diffuse large B-cell lymphoma (DLBCL). However, despite their success, CAR-T cell therapy still has limitations with treatment failure in more than half of the patients and severe therapy-related side effects, such as the cytokine release syndrome (CRS) and immune effector–cell associated neurotoxicity syndrome (ICANS). To improve therapeutic strategies, a better understanding of the relation of CAR-T cell dynamics with disease outcome and with the development of toxicity is needed. Here, we combined mathematical modelling of cell dynamics and clinical data to reveal how CAR-T cell response dynamics relates to patient progression and therapy success. To this end, we developed a mathematical model that accounts for the differentiation and proliferation of infused CAR- and non-CAR T cells, distinguishing between their various cellular subsets (i.e., naïve, central memory, effector memory) and correlating their cellular dynamics with clinical anti-tumoral efficacy and toxicity. Our model was applied to flow cytometry measurements of 79 DLBCL-patients treated by CAR-T cells at the University Hospital Erlangen and the LMU in Munich that were followed up to 140 days after therapy. Testing different model assumptions by using a non-linear mixed effects modelling approach to account for individual patient dynamics, our preliminary estimates indicate that responders and non-responders to CAR-T cell therapy differ in their T cell subset kinetics. Our approach provides a step towards a quantitative and mechanistic understanding of the complex intermingled dynamics of CAR-T cell proliferation, differentiation and anti-tumoral efficacy, and their role for therapy success and toxicity development. Identification of beneficial subsets would result in altered production pipelines and improved patient selection ultimately leading to improved therapeutic strategies.

Dynamics of multi-team cell fate decision networks

Kushal Haldar[1], Vaibhav Anand[2]

[1]University of Bonn, Germany; [2]Indian Institute of Science Education and Research Pune, India

Competition between distinct groups is fundamental to complex systems, from political coalitions and economic markets to gene regulatory networks (GRNs) controlling cell fate. Strikingly, cell-fate decision systems predominantly employ binary competition between two mutually inhibitory teams of genes, despite multi-team competition being common in social and ecological contexts. This raises a fundamental question: does binary decision-making offer functional advantages over multi-team systems? We systematically analyzed multi-team competitive networks using Boolean dynamics on signed directed graphs, extending well-characterized two-team GRN architectures to systems with three or more mutually inhibitory teams. Three-team networks produced significantly less stable outcomes than two-team systems, with steady states showing higher structural frustration and increased sensitivity to perturbations. Multi-team systems exhibited unpredictable transitions even under controlled perturbations, especially at lower densities typical of real networks. Networks with four or more teams failed to maintain distinct stable states entirely. Using spectral analysis, we show that team structure can be predicted from network eigenproperties, extending structural balance theory to directed signed networks. Our findings explain why binary decisions dominate biology and provide insights into coalition instability in social systems, market dynamics, and organizational structures. This work establishes fundamental stability principles for competitive networks across disciplines.

Making One Measurement Count: Efficient Dynamic Inference in Label-Based Models

Paul Jonas Jost, Jan Hasenauer

Bonn Center for Mathematical Life Sciences, University of Bonn, Bonn, Germany; LIMES Life and Medical Sciences Institute, University of Bonn, Bonn, Germany

Model-based analysis of metabolic labeling experiments offers a powerful way to extract dynamic information from systems where only destructive measurements are available. By leveraging multiple labeling states that are intrinsically linked through a shared biochemical dynamic, it becomes possible to infer temporal behavior from a single measurement, circumventing the need for longitudinal sampling. This modeling strategy, however, raises important questions about how labeling depth and model complexity affect the reliability and efficiency of parameter estimation. In this poster, we investigate how variations in labeling resolution and model simplification influence parameter inference in such single-measurement, multi-label frameworks. Using an identifiable toy model, we systematically construct simplified labeling variants by reducing the number of label states while maintaining the shared underlying dynamic. These controlled reductions enable us to assess the necessary level of labeling detail to accurately recover parameters and how inference behaves as structural complexity is removed. To complement these controlled experiments, we apply the same methodology to real lipidomics data. Across all model and labeling configurations, we perform parameter estimation under consistent optimization settings and evaluate both recovery accuracy and computational burden. We further analyze characteristic features of the optimization process, including convergence behavior and variability across repeated inference runs. Together, these analyses aim to clarify the trade-offs inherent in dynamic inference from destructive labeling experiments. By determining when simplified models and reduced labeling schemes remain informative—and when they compromise inference quality—we provide guidance for selecting appropriate model complexity and labeling depth. This contributes to more efficient use of experimental and computational resources while strengthening the interpretability and robustness of dynamic metabolic analyses based on single destructive measurements.

Disentangling Familial and Syndromic Facial Features Using Latent Embedding Analysis

Carolin Kaffiné[1], Aron Kirchhoff[1], Alexander Hustinx[1], Stefan Barakat[2,3], Elke Reutershahn[4], Davor Lessel[5], Annabelle Arlt[1], Peter Krawitz[1]

[1]Institute for Genomic Statistics and Bioinformatics, University Hospital Bonn, Bonn, Germany; [2]Department of Clinical Genetics, Erasmus MC University Medical Center, Rotterdam, The Netherlands; [3]Discovery Unit, Department of Clinical Genetics, Erasmus MC University Medical Center, Rotterdam, The Netherlands; [4]Department for Pediatrics, HELIOS St. Johannes-Klinik, Duisburg, Germany; [5]Institute of Clinical Human Genetics, University Hospital Regensburg, Regensburg, Germany

Introduction: Our genome contains many variants that shape familial facial similarity, yet even a single pathogenic nucleotide variant can cause a disorder-associated facial change that diverges from the family resemblance. AI-based next-generation phenotyping (NGP) tools like GestaltMatcher support diagnosis of rare genetic syndromes but typically ignore non-pathogenic familial resemblance, which can obscure syndrome-specific features. Familial traits, such as joined bushy eyebrows, may mimic characteristic similarities seen in rare disorders like Cornelia de Lange syndrome and thereby confound diagnosis. Addressing this challenge makes family or trio data particularly valuable for separating “signal” (syndromic morphology) from “noise” (familial variation).

Methods: We propose a framework that integrates unaffected family member portraits into the analysis of affected individuals. Facial embeddings derived from GestaltMatcher will be compared across trios and larger families to quantify latent similarity. Specifically, we will (1) analyze covariance structures between parental and affected individual embeddings, (2) project the individual embedding onto the subspace spanned by family members and use the residual vector as a candidate “syndromic component”, and (3) examine whether similarity in the embedding space reflects expected familial inheritance patterns. 40 families with confirmed pathogenic variants in DHX30, RNU4-2, and individuals affected by Williams-Beuren Syndrome are used as an initial dataset and proof-of-concept. Results: Initial analyses have focussed on quantifying how individual residual embeddings deviate from family baselines and have shown promising pre-results where the top-1-accuracy nearly doubled. Quantitative results are still pending since we are currently collecting more high-quality family portrait datasets of the above mentioned disorders, which can be uploaded here: https://www.gestaltmatcher.org.

Conclusion: By incorporating information about familial resemblance, this study aims to refine AI-driven facial phenotyping for rare genetic disorders. Modeling family structure directly within the embedding space could reduce false positive associations and emphasize syndrome-specific features. Ultimately, this approach is expected to reveal consistent patterns of familial covariance. It aims to delineate the boundary between pathogenic and normal phenotypic variation and inform future extensions of GestaltMatcher and related tools.

Finite Element Space-Time Total Generalized Variation Regularization with applications to transmembrane potentials in ECGI

Moritz Kappes[1], Manuel Haas[1], Simone Pezzuto[2], Alexander Effland[1]

[1]Institute for Applied Mathematics, University of Bonn, Germany; [2]Department of Mathematics, University of Trento, Italy

The noninvasive reconstruction of cardiac potentials from sparse torso measurements yields a highly ill-posed inverse problem, making accurate recovery of cardiac electrical activity challenging. We propose a novel joint spatio-temporal total variation (TV) regularization within a finite element framework to reconstruct transmembrane potentials. The method enables anisotropic smoothing across space and time while preserving sharp boundaries. Reconstructions are computed by a first-order primal-dual algorithm. Using simulated activation sequences on 2D/3D models, we compare our method to state-of-the-art zero- and first-order Tikhonov (T0/T1) regularization by multiple metrics. Our spatio-temporal TV regularizer improves cardiac potential reconstructions and outperforms T0/T1 methods in all test cases. The method enables anisotropic smoothing across space and time while preserving sharp boundaries. Further we explore the potential of the Total Generalized Variation regularizer, a higher-order method enabling smooth transition between regions. We present convergence results as well as applications to different problems in the ECGI setting.

Advancing Explainability in Machine Learning Models for Alzheimer's Disease Prediction

Charles M. Kaumbutha[1], Matthias Becker[2]

[1]Systems Medicine, DZNE, Bonn, Germany; [2]Modular High Performance Computing and Artificial Intelligence, DZNE, Bonn, Germany

Alzheimer's disease (AD) poses significant challenges for early diagnosis due to its heterogeneous progression and subtle preclinical symptoms. Early identification of individuals at risk is essential for timely interventions and effective disease management. This study utilises clinical metadata from the DELCODE cohort which is a longitudinal dataset designed to monitor cognitive decline. Here, we perform a multi-class classification across four cognitive stages: cognitively normal, subjective cognitive decline (SCD), mild cognitive impairment (MCI) and AD. First, we impute missing values by performing multiple imputation for the prediction task through imputing and running the analysis m times, across four classifiers – CatBoost, XGBoost, Random Forest and TabPFN – then pooling the predictions using Rubin's Rule. Using partial dependence plots (PDP) to examine the stability of imputations, our results show that features associated with cognitive scores produce stable imputations across the m datasets relative to biomarkers features. Second, we anchor our analysis on Explainability to evaluate the classifiers performances. Our initial analysis reveals that the predictive performances across the models, using discriminative metrics suited for class imbalance such as balanced accuracy and weighted f1, is marginal hence the extension of evaluation. Our results show while the models consistently agree along most of the feature attributions, mechanistic differences arise particularly when evaluating SCD and MCI classes. By assessing these differences, we highlight whether models align to clinically meaningful features across these disease stages. Our findings not only directly provide valuable insights for AD classification to the DELCODE study but also move towards developing models that are disease stage-appropriate and clinically trustworthy.

Tissue Microarray-Based Spatial Transcriptomics Defines TME in Cholangiocarcinoma

Tugberk Kaya

University Hospital Bonn, Germany; DZNE, Bonn, Germany

The cholangiocarcinoma (CCA) tumor microenvironment (TME), driven by cancer-associated fibroblasts (CAFs), is poorly defined, especially in metastasis. We employed a novel Xenium spatial transcriptomics workflow on a custom tissue microarray containing primary CCA and paired lymph node metastases. Spatial analysis with BANKSY revealed significant CAF heterogeneity, identifying two distinct CCL19+ and CXCL10+ subtypes. These subtypes occupy unique immunological niches: CCL19+ CAFs are proximal to T-cells, while CXCL10+ CAFs are spatially excluded. This highlights specific CAF-T-cell interactions as potential therapeutic targets to overcome immunosuppression in CCA.

APP-Driven Vaccine Design: A Quantitative Framework for Optimizing Epitope Presentation

Sahil Khan[1,2], Martin Pašen[1,2], Michele Mishto[3,4#], Juliane Liepe[1,5#]

[1]Max Planck Institute for Multidisciplinary Sciences, Göttingen, Germany; [2]Göttingen Graduate Center for Neurosciences, Biophysics, and Molecular Biosciences, University of Göttingen, Germany; [3]Centre for Inflammation Biology and Cancer Immunology (CIBCI) & Peter Gorer Department of Immunology, King's College London, London, United Kingdom; [4]Research group of Molecular Immunology, Francis Crick Institute, London, United Kingdom; [5]Facility for Data Sciences and Biostatistics, Max-Planck-Institute for Multidisciplinary Sciences, Göttingen, Germany

[#]shared last authorship

The presentation of tumor-associated antigens (TAAs) on HLA class I molecules is a critical step in the activation of $CD8^+$ T cells and the initiation of effective anti-tumor immune responses. In melanoma, one such TAA is glycoprotein 100 (gp100), which is processed via the antigen processing and presentation (APP) pathway. This involves proteasomal degradation of gp100 into peptide fragments, transport of these peptides into the endoplasmic reticulum (ER) via TAP, loading onto HLA-I molecules facilitated by the peptide loading complex, and subsequent trafficking to the cell surface. Despite this machinery, natural immune responses against gp100-derived epitopes often fail to elicit sufficient $CD8^+$ T cell activation to control tumor growth. To enhance immunogenicity, peptide-based cancer vaccines have been developed. A notable example is the $gp100_{209-217}$(T210M) epitope (IMDQVPFSV), a modified version of the parental $gp100_{209-217}$ epitope (ITDQVPFSV), designed to improve binding affinity to HLA-A*02:01 while retaining recognition by T cell receptors (TCRs) specific for the original sequence. Although clinical trials have demonstrated promising results when this variant is combined with immune adjuvants, the mechanistic basis for its enhanced efficacy remains incompletely understood. Specifically, it is unclear whether improved HLA-I binding alone accounts for the increased $CD8^+$ T cell response or whether other components of the APP pathway contribute significantly. To address this, we developed a mechanistic mathematical model of the APP pathway, incorporating key molecular processes including proteasomal cleavage, TAP transport, peptide-HLA binding, and surface expression and recognition. The model was calibrated against quantitative data from in vitro reconstitution experiments through a Bayesian inference framework to account for experimental variability and ensure robust parameter estimation. Model predictions were validated against perturbation experiments, demonstrating good agreement across multiple conditions. Comparative simulations between the parental and variant epitopes confirmed that the T210M substitution enhances HLA-A*02:01 binding and overall epitope presentation. Importantly, the model showed that increased presentation efficiency—driven by greater epitope stability with HLA-A02:01 and stronger affinity for TAP—more than compensated for the slight decrease in TCR binding, resulting in a net gain in $CD8^+$ T cell activation potential. Sensitivity analysis further identified key bottlenecks in the APP pathway as critical factors influencing epitope presentation. These insights provide a rational basis for selecting and engineering epitopes with optimal immunogenic profiles. Our integrated experimental-modelling framework offers a tool for dissecting the molecular determinants of antigen presentation and guiding the design of next-generation peptide vaccines. By enabling quantitative comparisons of epitope variants and identifying rate-limiting steps in the APP pathway, this approach can be extended to other TAAs and applied to diverse cancer types. Ultimately, such mechanistic models hold promise for informing immunotherapeutic strategies in oncology.

A Cascade Framework for Quantifying the Operational Effectiveness of Insecticide-Treated Nets (ITNs) in Benin.

Agbatan Fiacre Luc Kouderin[1,2], Clara Champagne[3,4], Corine Ngufor[5,6,7]

[1]African Institute for Mathematical Sciences (AIMS), Kigali, Rwanda; [2]Hausdorff Center for Mathematics, University of Bonn, Bonn, Germany; [3]Swiss TPH, Allschwil Switzerland; [4]University of Basel, Basel, Switzerland; [5]London School of Hygiene and Tropical Medicine (LSHTM), London, UK; [6]Centre de Recherches Entomologiques de Cotonou (CREC), Cotonou, Benin; [7]Pan African Malaria Vector Research Consortium (PAMVERC), Cotonou, Benin

Background: Malaria continues to pose a significant health burden in Benin, where Insecticide-Treated Nets (ITNs) are the cornerstone of vector control. However, the real-world operational effectiveness of ITNs is often far lower than their theoretical entomological efficacy due to factors like physical degradation, insecticide decay, and human behavior. Quantifying the impact of these real-world limitations is critical for informing public health policy. Methods: We adapted an effectiveness cascade framework to model the performance of ITNs in the specific context of Benin. First, we estimated key entomological efficacy parameters (e.g., deterrency, pre/post-prandial killing) by fitting a Bayesian hierarchical multinomial model to four extensive Experimental Hut Trial (EHT) datasets from Covè, Benin. This model was implemented in Stan. Posterior samples of these parameters were then used to compute the proportional reduction in vectorial capacity induced by the nets. Finally, we constructed a 5-scenario cascade model to sequentially quantify the loss of impact. This framework integrates the entomological efficacy with operational and behavioral parameters derived from literature and national surveys, including net attrition (modeled with a Weibull decay function), net usage, insecticide decay, and human-vector behavioral mismatch. Results: Our analysis confirmed that next-generation nets demonstrate superior entomological efficacy compared to pyrethroid-only ones. However, the cascade analysis revealed the critical impact of real-world bottlenecks. Across all evaluated net types, from standard pyrethroids to dual-AI products, final operational effectiveness was reduced by approximately 40 to 60 percentage points from its theoretical maximum potential. Our model consistently identified two primary drivers for this decline: the physical durability of the net and the ITN usage by the population. These operational factors often accounted for a larger loss of effectiveness than the chemical decay of the insecticide itself. Conclusion: This work provides a tailored, model-based evidence base for Benin's National Malaria Control Program. Our framework serves as a practical decision-support tool, highlighting that procurement strategies must prioritize proven physical robustness and strategies to improve usage alongside insecticidal potency to maximize public health impact.

A data-integrated framework for modeling cellular interactions with semi-Markov dynamics

Rosa Kreider[1], Janhavi Prahbu[1], Joanna Schnorr[1], Wasiur R. KhudaBukhsh[2], Thomas Zillinger[1], Gunther Hartmann[1], Kevin Thurley[1]

[1]University Hospital Bonn, Germany; [2]University of Nottigham, UK

Mathematical modeling of cell interactions is essential for understanding dynamics of cellular systems such as the immune response. These interactions involve multiple scales, as cell state transitions are driven by complex intracellular biochemical processes. Capturing these dynamics requires models that allow flexible holding times between state transitions, which conflicts with classical Markovian modeling frameworks. Utilising the linear chain trick, we incorporate two-parametric Erlang distributions into rate-equation models and apply it to various biological applications. In particular, we analyze immune cell priming as a mechanism that gives rise to the characteristic optimal curve observed between the strength of viral infection and interferon secretion. This mechanism accounts for the ability of plasmacytoid dendritic cells to sustain high IFNα production even at low viral loads. Furthermore, we present an analytical modeling framework that exactly captures the mean dynamics of semi-Markov processes with arbitrary holding time distributions. Starting from stochastic first principles, we derive a closed-form deterministic framework suitable for direct comparison with experimental data. Through simulations of specific network motifs within cellular systems with different holding time distributions, we show that the choice of distribution has a substantial impact on the system's behavior. Our framework provides a generalized and analytically tractable approach for modeling non-Markovian cell dynamics and linking it to cellular kineatic data.

Integrative Single-Cell Modeling and TCR Repertoire Profiling Reveal a Sleep-Immune-Brain Axis in Early Alzheimer's Disease

Sophia Krix[1,2], Neus Falgàs[3], Andrea del Val-Guardiola[3], Sarah Hücker[4], Raquel Sanchez-Valle[3], Stefan Kirsch[4], Kuti Baruch[5], Holger Fröhlich[1,2,6]

[1]Department of Bioinformatics, Fraunhofer Institute for Algorithms and Scientific Computing (SCAI), Sankt Augustin, Germany; [2]Bonn-Aachen International Center for Information Technology (b-it), University of Bonn, Bonn, Germany; [3]Alzheimer's Disease and Other Cognitive Disorders Unit, Neurology Service, Hospital Clínic de Barcelona, Fundació de Recerca Clínic Barcelona-Institut d'Investigacions Biomèdiques August Pi i Sunyer (FCRB-IDIBAPS), University of Barcelona, Barcelona, Spai; [4]Division Personalized Tumor Therapy, Fraunhofer Institute for Toxicology and Experimental Medicine ITEM, Regensburg, Germany; [5]ImmunoBrain Checkpoint Ltd., Rechovot, Israel; [6]Institute for Digital Medicine, University Hospital Bonn, Bonn, Germany

Objectives: We investigated immune dysregulation in peripheral blood during the Alzheimer's disease (AD) continuum and explored how intracellular changes relate to sleep disturbances, neuroinflammatory signals, brain structure, and cognition. In a single-site cohort study of 79 participants (26 cognitively unimpaired, 25 with mild cognitive impairment, 28 with mild Alzheimer's dementia), we profiled PBMCs using 10X 5'RNA-seq jointly with V(D)J T-cell receptor (TCR) sequencing and integrated these data with 10-day actigraphy, clinical sleep scales, neuroinflammatory cerebrospinal fluid cytokines and noradrenaline, MRI volumes, cognitive batteries, demographics, and ApoE genotype. Methods: Major PBMC lineages were annotated by Azimuth, followed by subclustering of monocytes, Natural Killer cells, and CD8+ T cells. Differential expression testing was performed via donor-aware pseudobulk modeling, and enrichment was interpreted with GSEA. To obtain compact cell-state features, we learned a 10-dimensional latent representation using a conditional variational autoencoder over a curated set of 38 immune-related KEGG/Reactome pathways. For TCR repertoire analysis, clonal expansion and subcluster clonal proportions, diversity, V(D)J segment usage and CDR3 properties were analysed. We also quantified clonotype occupancy and expansion across T cell subclusters to link these repertoire metrics to functional states. Subject-level features for multimodal modeling comprised immune pathway enrichments, clonotype statistics, sleep metrics from actigraphy and questionnaires, CSF cytokines and noradrenaline, MRI-derived hypothalamus, locus coeruleus, and global gray matter volumes, cognitive domain scores, demographics, and ApoE. Directed relationships among these variables were inferred using a nonlinear, gradient based directed acyclic graph (DAG) learning approach with additive parent-wise functions and sparsity regularization under an explicit acyclicity constraint; edge stability was assessed with 100 bootstrap resamples while treating age, sex, and ApoE as exogenous covariates. Results: Immune dysregulation was most pronounced at the MCI stage, with monocytes, CD8+ T cells, and Natural Killer cells showing pathway-level perturbations in inflammatory cytokine signaling, antigen processing, and differentiation programs; several signals attenuated or reversed in dementia, consistent with compensatory or exhaustion dynamics. Subcluster analysis revealed differential expression in the MCI stage of certain CD8+ T cell, Natural Killer cell and monocyte subpopulations. Marker signatures were derived for subpopulations indicative of an MCI stage. Exact αβ clonotyping showed altered repertoire organization across stages, with expanded clones preferentially occupying subtypes of CD8+ T cells and stage-dependent changes in diversity indices, indicating modified antigen engagement. The putative causal graph linked sleep metrics—particularly sleep efficiency, fragmentation, and regularity—to immune latent variables, which in turn connected to domain-specific cognitive performance, suggesting a directed sleep–immune–brain axis that evolves across disease stages. Conclusion: We coupled single-cell representation learning, donor-aware differential analysis, exact αβ clonotype statistics, and nonlinear causal graph inference to move beyond association toward mechanism. Our results reveal a stage-evolving sleep–immune–brain axis in Alzheimer's disease with downstream cognitive effects, identifying candidate mediators and mechanistic targets— actigraphy-derived sleep quality metrics and peripheral immune system dysregulation—as actionable readouts for early stratification and therapeutic monitoring.

Random Walks or Directed Paths? – Harvesting the Potential of 3D Modeling to Uncover the Impact of Ontogeny on Alveolar Macrophage Dynamics

Michelle Krogemann[1,2], Simon Merkt[1,2,3], Ana Ivonne Vazquez-Armendariz[2], Jan Hasenauer[1,2]

[1]Bonn Center for Mathematical Life Sciences, Bonn University, Bonn, Germany; [2]Life and Medical Sciences Institute, Bonn University, Bonn, Germany; [3]Institute of Innate Immunity, Medical Faculty, Bonn University, Bonn, Germany

Macrophages are key components of the innate immune system and play essential roles in maintaining tissue integrity and defending the body against infection and injury. Among them, alveolar macrophages occupy a particularly critical position as they reside at an interface between the body and the external environment, forming a major line of defense within the respiratory system. These cells can be broadly classified according to their developmental origin into two major populations: lung resident macrophages derived from embryonic yolk sac progenitors, and bone marrow derived macrophages that are recruited in response to infection or inflammation. They also exhibit distinct functional specializations: yolk sac derived alveolar macrophages are primarily involved in long term tissue maintenance and homeostasis, whereas bone marrow derived macrophages contribute mainly to inflammatory responses and tissue repair. Beyond their ontogeny, these populations differ in their life span, gene expression, and metabolic profiles. A suitable approach to investigate macrophage migration dynamics is the use of organoid systems, as they combine relative experimental accessibility with a realistic representation of tissue architecture. Such systems enable the investigation of migration dynamics, allowing comparison between two temporally distinct migration events: bone marrow derived macrophages, which continuously replenish the macrophage population in the adult lung, and yolk sac derived macrophages, which migrate to the alveolar surface during embryonic development. Building on the known differences of alveolar macrophages, this project aims to explore whether the distinct origins also translate into different migration behaviors. Unravelling differences in randomness or directedness of the movement could provide new insights into how macrophage dynamics contribute to tissue homeostasis and immune responses in the lung. For this purpose, a computational modeling framework will be developed based on live cell imaging data of yolk sac derived and bone marrow derived alveolar macrophages. The data are generated using a BronchioAlveolar Lung Organoid system that reproduces key structural and cellular features of lung tissue and allows observation of macrophage migration in a physiologically relevant environment. Two experimental conditions will be analyzed: unstimulated organoids to represent homeostasis, and lipopolysaccharide stimulated organoids to mimic inflammation induced by injury or infection. Image processing and analysis will be performed using software such as Fiji and IMARIS to identify and track individual macrophages, extract velocity data, and quantify spatiotemporal distribution patterns within the organoid. These data will form the basis for training and adjusting a mathematical model that can describe macrophage dynamics over time and space. Diffusion-reaction-drift equations will be used to model macrophage migration. By fitting the model separately for each macrophage population and condition, differences in the degree of directed versus stochastic movement can be quantified. By integrating quantitative imaging data with mathematical modeling, this work seeks to provide a mechanistic understanding of how macrophage origin and inflammatory stimulation shape migration patterns in the alveolar environment. The developed computational model will serve as a tool to generate and test hypotheses on macrophage behavior in health and disease, contributing to a deeper understanding of immune cell dynamics in lung tissue.

NephrESA: Machine learning-informed mechanistic mathematical modelling to optimize anaemia treatment

Nantia Leonidou[1]*, Clara Hennersdorf[1]*, Agustin Rodriguez Gonzalez[1], Anand Ruban Agarvas[2], Rafael Arutjunjan[3], Tiago J. S. Lopes[2], Elisabeth Meister[4], Ujjwal Yadav[1], Christina Mertens[2], Martina U. Muckenthaler[2], Tobias B. Huber[4], Andreas Raue[5], Marcel Schilling[1], Jens Timmer[3], Ursula Klingmüller[1]

[1]Systems Biology of Signal Transduction (B200), German Cancer Research Center (DKFZ), Heidelberg, Germany; [2]Center For Translational Biomedical Iron Research, Department of Pediatric Hematology, Oncology Immunology and Pulmonology, Heidelberg University Hospital, Germany; [3]Institute of Physics, University of Freiburg, Germany; [4]III. Department of Medicine, University Medical Center Hamburg-Eppendorf, Germany; [5]University of Augsburg, Germany

*shared first authorship

Anemia is characterized by a reduced number of red blood cells (erythrocytes containing hemoglobin and is a common complication of chronic kidney disease (CKD) and cancer. In CKD, anemia results from impaired erythropoietin (Epo)-receptor binding in the bone marrow, while in cancer it arises from inflammation, nutritional deficiencies, bone marrow suppression, and treatment effects. Erythropoiesis-stimulating agents (ESAs) are used in both conditions; however, despite guideline-based therapy, dialysis CKD patients we observed hemoglobin fluctuations due to unaccounted patient-specific factors, increasing hemodynamic stress and the risk of thromboembolic and cardiovascular events.

To address such treatment-induced instability, we developed a machine learning–informed, mechanistic multiscale mathematical modeling framework. For model calibration, we collected longitudinal clinical data from over 200 healthy individuals as well as over 1,500 lung cancer and CKD patients, including time-resolved measurements of hemoglobin (Hb) and ESA administration. Using this data as input for parallel tree boosting machine learning algorithms, we identified key features associated with anaemia and haemoglobin levels forming the basis for a mechanistic ordinary differential equation (ODE) and mixed effects model capable of capturing and predicting anemia trajectories. While most model parameters could be fixed globally, three were identified as patient-specific: the number of ESA binding sites, the hemoglobin degradation rate, and the initial hemoglobin concentration.

Altogether, these results provide the basis to develop a decision support tool that aims to stabilize haemoglobin levels in patients, thereby lowering the risk of thromboembolic events, and reducing ESA treatment costs. To support clinical integration, we are currently focusing on real-time data retrieval, analysis and potential clinically relevant model extensions. We opt for delivering therapy recommendations within minutes, enabling precision dosing for maintaining erythropoietic homeostasis, and improve the quality of life of chronically diseased patients.

Transcriptome-structured population models for neural stem cells

Carolin Lindow, Anna Marciniak-Czochra

Heidelberg University, Germany

Adult neurogenesis represents the generation of neurons from neural stem cells, which have been known to be in two states: active and quiescent, given by whether they are in the cell cycle or not, respectively. Single-cell RNA-sequencing data of the neural lineage shows a variation in gene expression among quiescent neural stem cells (qNSCs), suggesting the possibility of a continuum of qNSCs states in the transcriptome space. Inspired by this heterogeneity, we study the influence of the gene activation profile on the dynamics of neurogenesis using structured population models. To describe discrete and continuous transitions between cell states as well as the complicated underlying topological structure of the high-dimensional gene space obtained from experiments, we use structured population models on the space of Radon measures. The model we study represents the quiescent neural stem cells on a continuum from deep to shallow quiescence that represents the pseudo-time axis that is often fitted to time snapshots of single-cell RNA sequencing data. Cells can move along this path and can be recruited to the compartment of active cells which proliferate. The cells resulting after division either differentiate into progenitor cells or return to quiescence. It is of particular interest to see how the additional structure from the continuity of the gene activation states of the quiescent neural stem cells influences the dynamics of neurogenesis. Namely, we study how cells move on the continuum, how the activation rate of the cells changes with the gene expression, and which genes a cell expresses upon its return to quiescence. We analyze the effects of these model choices on the total number of cells as well as on the distributions of cells in the state space.

Catalyst: Fast and flexible modeling of reaction networks

Torkel Loman[1], Vincent Du[2], Yingbo Ma[3], Vasily Ilin[4], Shashi Gowda[5], Niklas Korsbo[6], Nikhil Yewale[7], Chris Rackauckas[5], Samuel Isaacson[8]

[1]University of Oxford, UK; [2]University of North Carolina at Chapel Hill, USA; [3]JuliaHub; [4]University of Washington, USA; [5]MIT, USA; [6]Pumas.AI; [7]Indian Institute of Technology Madras, India; [8]Boston University, USA

Chemical reaction networks (CRNs) are a commonly used model type in biology and chemistry (with applications in e.g. systems biology, pharmacology, and epidemiology). Here, we demonstrate Catalyst.jl, a flexible and feature-filled Julia library for the creation, simulation, and analysis of CRN models. Models can be created both using the Catalyst DSL (which enables the implementation of CRNs in their native reaction format), or built programmatically. Next, they can be simulated using ODE, SDE, and jump process (e.g. Gillespie simulation) approaches. Internally, models are represented symbolically, enabling e.g. automatic symbolic simplifications and Jacobian constructions to improve simulation performance. Finally, Catalyst's internal CRN model representation enables it to compose with many additional modelling packages. This facilitates features such as steady state computations, bifurcation analysis, identifiability analysis, and parameter fitting.

Determining viral spread and innate immune dynamics in human respiratory epithelium

Pascal Lukas[1], Aurélien Gibeaud[2], Clarisse Schumer[3], Jonas Arruda[4,5], Jeremie Guedj[3], Olivier Terrier[2], Frederik Graw[1,6,7]

[1]Department of Internal Medicine 5, Haematology and Oncology, Friedrich-Alexander-Universität Erlangen-Nürnberg and Universitätsklinikum Erlangen, Erlangen, Germany; [2]CIRI, Centre International de Recherche en Infectiologie, Team VirPath, Université Lyon-1, Inserm U1111, CNRS and ENS de Lyon, Lyon, France; [3]IAME, Université Paris Cité, Université Sorbonne Paris Nord and Inserm, Paris, France; [4]Bonn Center for Mathematical Life Sciences, University of Bonn, Germany; [5]Life and Medical Science Institute, University of Bonn, Germany; [6]Deutsches Zentrum Immuntherapie (DZI), Erlangen, Germany; [7]Bavarian Cancer Research Centre (BZKF), Erlangen, Germany

Understanding the mechanisms that govern viral spread in human airway epithelium (HAE) remains a major challenge, particularly with regard to identifying and quantifying key factors such as cell-type-specific infectivity, viral transmission pathways, and innate immune dynamics. Although mathematical models and experimental advances have provided valuable insights into respiratory viral infections, revealing the complex spatio-temporal interactions of infection and immune processes on a tissue-level have remained elusive. Here, we present an innovative workflow that combines time-resolved bulk measurements and spatially explicit image information to allow the inference of viral and immune kinetics within HAE for various respiratory viruses. While standard inference methods typically require custom summary statistics and resourceful fitting procedures for each individual data set, our workflow relies on the combination of different simulation-based trained neural networks within BayesFlow, a framework of neural posterior estimation. This framework allows for amortized inference and the integrative analysis of various types of data. To this end, invertible neural networks (INNs) are trained based on simulated data that comprise time-resolved bulk measurements and spatially explicit image information, thereby individually learning appropriate summary features that are associated with particular viral and immune kinetics. These trained networks are then inverted and applied to actual experimental data and measurements to infer viral and innate immune kinetics for various respiratory viruses. We validated our approach by synthetic data simulating viral infection dynamics in HAE using systems of increasing complexity that account for tissue heterogeneity, cell-type specific infection and turnover kinetics, as well as interferon-mediated immune responses, with generated data mirroring experimental measurements accounting for disrupted sampling, i.e., not being able to follow the same culture over time. Thereby, we could show that integrating spatial information is essential to reliably infer viral transmission kinetics and innate immune interactions. Applying our approach to experimental data on SARS-CoV-2 infection dynamics within HAE culture systems, we estimated that the majority of all infections were due to cell-associated transmission, pointing towards local transmission as the dominant mode of SARS-CoV-2 spread within HAE. Our approach can be readily applied to HAE culture systems for inference of viral and innate immune kinetics of different respiratory viruses, like IAV, SARS-CoV-2 and RSV, allowing multi-modal data integration without the need for frequent resourceful re-fitting approaches and the identification of viral-specific infection patterns and kinetics. In summary, the presented workflow provides a computationally efficient and biologically insightful general framework to assess viral and immune dynamics within tissues for a diverse range of viral infections by integrating longitudinal bulk and spatially-resolved measurements.

ConvexGating infers gating strategies from clusters in single cell cytometry data

Vincent D. Friedrich[1,2], Karola Mai[3,4], Thomas P. Hofer[5], Elfriede Nößer[5], Lorenzo Bonaguro[3,6,7], Celia L. Hartmann[3,8], Aleksej Frolov[3,8,9], Caterina Carraro[3,6], Doaa Hamada[3,10,11], Mehrnoush Hadaddzadeh-Shakiba[3,8], Heidi Theis[7], Markus Scholz[1,12], Fabian J. Theis[13,14,15], Matthias Becker[3,4], Marc D. Beyer[3,7,8], Joachim L. Schultze[3,6,7], Maren Büttner[3,7,13]

[1]University of Leipzig, Institute for Medical Informatics, Statistics, and Epidemiology, Leipzig, Germany; [2]Center for Scalable Data Analytics and Artificial Intelligence (ScaDS.AI), Leipzig, Germany; [3]Systems Medicine, German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany; [4]Modular High Performance Computing and Artificial Intelligence, German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany; [5]Research Group Tissue Control of Immunocytes, Helmholtz Center Munich, Munich, Germany; [6]Life and Medical Sciences (LIMES) Institute, University of Bonn, Bonn, Germany; [7]PRECISE Platform for Single Cell Genomics and Epigenomics, DZNE and University of Bonn and West German Genome Center (WGGC), Bonn, Germany; [8]Immunogenomics & Neurodegeneration, German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany; [9]Department of Microbiology and Immunology, The Peter Doherty Institute for Infection and Immunity, University of Melbourne, Melbourne, VIC, Australia; [10]Molecular Immunology in Neurodegeneration, German Center for Neurodegenerative Diseases and the University of Bonn, Germany; [11]Medical Microbiology and Immunology Department, Faculty of Medicine, Mansoura University, Egypt; [12]University of Leipzig, Faculty of Mathematics and Computer Science, Leipzig, Germany; [13]Institute of Computational Biology, Helmholtz Center Munich, Germany; [14]Department of Mathematics, Technical University of Munich, Germany; [15]TUM School of Life Sciences Weihenstephan, Technical University of Munich, Germany

Manual expert gating remains the standard approach for defining cell populations in flow cytometry, yet this practice faces critical limitations as datasets grow in complexity. The expanding number of markers per cell, combined with substantial inter-rater variability, renders manual gating increasingly inconsistent, which is particularly problematic in large-scale and multi-center studies. To address these challenges, we present ConvexGating, a data-driven computational method that automatically infers gating strategies in an unbiased, data-driven, and interpretable manner. ConvexGating models cell populations as convex regions in multidimensional marker space, with boundaries defined by hyperplanes that enclose cells of interest. This geometric approach scales efficiently with increasing dimensionality while maintaining full interpretability. The algorithm iteratively optimizes gate placement through regularized gradient-based learning, using the F1 score to balance precision and recall. Unlike hierarchical manual gating, ConvexGating infers population boundaries directly from data without dependence on predefined parent populations. The method generates precise, reproducible gating strategies that transfer directly to laboratory cell sorters. We experimentally validated the inferred gates for $CD8^+$ naïve and TEMRA cells using single-cell RNA sequencing (scRNA-seq), achieving more homogeneous sorted populations than conventional approaches. ConvexGating also enables identification of both well-characterized populations and previously undefined or poorly characterized subsets, as we demonstrate by fully defining plasmacytoid dendritic cells (pDCs) as $CD57^-$ $CD13^-$ $CD45RA^+$ $CD123^+$. Our work extends beyond flow cytometry to CyTOF and CITE-seq data, providing a unified computational framework across cytometry modalities. Additionally, it supports optimal marker panel design by identifying marker combinations that yield the most informative gating strategies, guiding experimental design in a data-driven manner. By integrating mathematical modeling, optimization, and rigorous biological validation, ConvexGating bridges computational inference with experimental practice. It offers a robust, scalable, and interpretable solution for automated cell population identification and sorting that advances reproducibility and efficiency in high-dimensional cytometry workflows.

Design principles of interferon signaling in regulating cell-density-dependent behavior under Type 1 diabetes scenario

Liza Zamashanski[1], Madhuri Majumder[2,3], Agnes Klochendler[1], Einat Shaer Tamar[2,3], Yuval Dor[1#], Miri Adler[2,3#]

[1]Department of Developmental Biology and Cancer Research, Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel; [2]Department of Genetics, Silberman Institute of Life Sciences, Hebrew University of Jerusalem, Jerusalem, Israel; [3]Department of Immunology and Cancer Research, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel

[#]shared last authorship

Type 1 diabetes is marked by chronic interferon (IFN)-driven islet inflammation and progressive beta (β)-cell loss. A central question is why β cells, but not alpha (α) cells, are particularly susceptible to IFN-mediated pathology. Genetic studies show that ADAR (Adenosine Deaminase Acting on RNA) knockout in β cells elicits strong IFN responses, inflammation, and metabolic dysfunction, whereas α-cell ADAR knockout induces only a weak IFN signal without inflammation. The cause of this disparity remains unclear. Experimental evidence reveals that IFN activation in α cells depends on cell density and metabolic state. High-density clusters can surpass an activation threshold, triggering full IFN induction and immune recruitment due to close cell–cell interaction. Moreover, metabolic stress—such as glucagon receptor antagonism or palmitate exposure-enables α cells to mount stronger IFN responses, indicating that metabolism modulates IFN levels. It seems that cell density plays a significant role in regulating the inflammatory response. However, the regulatory mechanism underlying this behavior remains unknown. To mechanistically explain these observations, we hypothesized that IFN signaling operates through a positive feedback loop: the more IFN a cell senses, the more it produces. We first built an ordinary differential equation (ODE) model of IFN dynamics incorporating this self-amplifying loop. The model exhibited bistability, with a low-IFN stable state, a high-IFN stable state, and an intermediate unstable threshold. This architecture predicts switch-like behavior, where small increases in stimulation can drive an abrupt transition from quiescence to full activation. To extend this framework spatially, we developed an agent-based model simulating individual cells producing and sensing diffusible IFN. Each cell's feedback strength and neighbourhood density determined whether it crossed the activation threshold. The simulations revealed that low-density producers remain below threshold, while dense clusters transition collectively into a self-sustaining inflammatory state. Once the fraction of active cells exceeded a critical density, total IFN levels rose sharply, consistent with bistable switching. Introducing metabolic stress by elevating basal IFN production further pushed the system toward activation, lowering the density threshold required for switching. Parameter screening confirmed that higher basal production and feedback gain enhance IFN persistence, recapitulating the stronger inflammatory phenotype observed under metabolic stress. Together, these integrated experimental and modeling approaches reveal design principles by which positive feedback, metabolism, and spatial organization jointly govern IFN signaling in islets. This framework provides a mechanistic explanation for the selective vulnerability of β cells, which may reside in conditions favoring sustained IFN amplification. By identifying how metabolic activity and feedback loops tune IFN thresholds, this study highlights potential therapeutic strategies to prevent chronic β-cell inflammation in diabetes.

Mathematical Modeling of Neuroblastoma Growth Based on Tumoroid data

Perla Mallouk, Fabien Crauste

Université Paris Cité, CNRS, MAP5, Paris, France

Neuroblastomas are solid tumors and represent the most common extracranial tumors in children, with no known cause to date. The analysis of tumoroid data (artificial organoids capable of reproducing neuroblastoma growth) has revealed a distinctive spatial organization: cancer stem cells tend to cluster at the center of the tumor. A multiscale agent-based neuroblastoma tumoroid model was developed to simulate neuroblastoma growth. Data provided by this computational model represent a unique opportunity to investigate the genetic causes of neuroblastoma tumors' spatial structures. Our goal is to build a mathematical model that can reproduce the growth of neuroblastoma based on these data, in order to better understand and capture the particular spatial distribution as the result of the stochastic interaction of genes promoting stem or differentiated phenotypes and non-local interactions based on gene dynamics, and ultimately propose more targeted treatments. We combined an existing deterministic model of tumor growth, which accounts for cell proliferation, diffusion, and differentiation, with a Piecewise Deterministic Markov Process (PDMP) representing the stochastic gene regulatory network. We conducted a mathematical analysis of this model to prove that it is well-posed, using semigroup theory and stochastic process theory. We also performed numerical simulations in both 1D and 2D to observe whether the expected spatial distribution emerges. Results show that cell proliferation and diffusion occur as expected for each cell type, but the specific clustering of stem cells is not yet reproduced. The model needs to be further refined to better capture this spatial organization, which will be the focus of the next steps of this work. This work has been done in collaboration with Olivier Gandrillon (Inria, ENS de Lyon) and Thi Nhu Thao Nguyen (Université Paris Cité, Inria, ENS de Lyon).

Segmentation Strategies for Spatial Transcriptomics in Murine Adipose Tissue

Simon Merkt[1,2,3], Paul Maier[1], Andreas Schlitzer[1]

[1]Life and Medical Science Institut (LIMES), University of Bonn, Bonn, Germany; [2]Institute of Innate Immunity (III), University Clinics Bonn, Bonn, Germany; [3]Bonn Center for Mathematics and Life Sciences (BCML), University of Bonn, Bonn, Germany

Imaging-based spatial transcriptomics platforms like Xenium enable subcellular-resolution mapping of gene expression alongside tissue morphology. A critical step in these analyses is cell segmentation—assigning transcripts to individual cells—using either image-based features or transcript distributions. Segmenting adipose tissue presents distinct challenges: adipocytes are large, with nuclei and transcripts confined to a thin peripheral rim due to central lipid droplets, while immune cells are small, densely packed, and transcriptionally active throughout. In this ongoing study, we assess segmentation strategies for Xenium data from murine adipose tissue. We benchmark several methods, including the Xenium default segmentation, the transcript-guided ProSeg model, the convolutional-neural-network-based Cellpose, and the transformer-based Cellotype. Preliminary results indicate that Cellotype performs well in capturing large adipocytes and resolving surrounding immune cells. However, its performance varies across regions, especially where staining is weak or cell boundaries overlap. To overcome these limitations, we are investigating a hybrid approach that applies Cellotype where morphology is informative and incorporates transcript guided methods elsewhere. Our results underscore the importance of flexible, tissue-adapted segmentation strategies for spatial transcriptomics, particularly in complex tissues like adipose, where cell size and structure vary substantially.

Identifiability Analysis of Foundational Cardiac Electrophysiology Models: The Noble Model

Josua Michael[1], Simon Beyer[1], Jens Timmer[1], Viviane Timmermann[1,2]

[1]Institute of Physics, Albert-Ludwigs-University Freiburg, Germany; [2]Institute of Molecular Medicine and Cell Research, Albert-Ludwigs-University Freiburg, Germany

Background Cardiovascular diseases remain the leading cause of death worldwide.[1] Mathematical models of cardiac electrophysiology have become invaluable in understanding their underlying mechanisms. Building on the pioneering work by Hodgkin and Huxley (1952),[2] Noble (1962) was the first to apply Hodgkin-Huxley like formulations to cardiac Purkinje fibers, laying the foundation for a long tradition of biophysical cardiomyocyte models.[3] Over time, these models have grown increasingly complex, consisting of large systems of coupled ordinary differential equations, that integrate data across different laboratories, species, and experimental conditions. However, their expanding dimensionality often leads to parameter redundancy and non-identifiable model behaviour, challenging mechanistic interpretation. Methods We use a dual-likelihood approach, involving maximum-likelihood estimation followed by profile-likelihood analysis, to assess the structural and practical identifiability of cell models of cardiac electrophysiology. This framework allows us to quantify parameter uncertainties and assess effectiveness of experimentally observed model constrains. As a proof of concept, we perform a comprehensive identifiability analysis of the established Noble-Model using the dMod package in R von Kaschek et al. (2019).[4] Outlook Our goal is to determine identifiability as a central diagnostic tool in theoretical cardiology in order to improve explanatory power of cardiac myocyte models. This bottom-up investigation starts with the most basic cardiac myocyte model and may help to clarify whether the initial formulations by Hodgkin-Huxley, and Noble, remain valid, or if more recent formulations of cardiac electrophysiology are needed to be reevaluated.

1. World Health Organization. Cardiovascular diseases (CVDs). 2023. https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-%28cvds%29
2. Hodgkin AL, Huxley AF. A quantitative description of membrane current and its application to conduction and excitation in nerve. *J Physiol*. 1952;117(4):500-544. doi:10.1113/jphysiol.1952.sp004764
3. Noble D. A modification of the Hodgkin--Huxley equations applicable to Purkinje fibre action and pace-maker potentials. *J Physiol*. 1962;160(2):317-352. doi:10.1113/jphysiol.1962.sp006849
4. Kaschek D, Mader W, Fehling-Kaschek M, Rosenblatt M, Timmer J. Dynamic Modeling, Parameter Estimation, and Uncertainty Analysis in R. *J. Stat. Soft*. 2019;88:1-32. doi:10.18637/jss.v088.i10

Model Based Analysis Of The Mutational Landscape In Antibody Affinity Maturation

Robin Müller, Kevin Thurley

Institute of Experimental Oncology, University Hospital Bonn, Germany

The human immune system protects the body against a wide range of diseases. To adapt its responses to diverse antigens, B cells undergo the cyclic affinity maturation process within germinal centers inside secondary lymphoid organs. During this process, they alternate between mutating their genes responsible for antigen binding and competing for T-cell proliferation signals, being selected according to acquired antigen-binding affinities. The accumulation and interplay of mutations drive this process. Although recently developed techniques have enabled data-driven analyses of affinity landscapes[1] and revealed epistatic effects,[2,3] a systematic, model-based analysis is still warranted to clarify the mechanisms guiding B cells towards sufficient binding affinity. We therefore developed a stochastic simulation framework for affinity maturation (SAM), extending an established Markovian model[4] to a discrete genotype space and asserting genotype specific fitness scalars according to antigen-binding affinity. By applying and extending heterogeneity measures of this mutational landscape on varying scales, ranging from the global NK model to recently applied local γ-statistics, we aim to characterise its influence on the fixation times of affine genotypes, the distribution of mutational trajectories taken, and their stochastic variability to determine structural properties enhancing and limiting the maturation process. This framework provides a quantitative basis for understanding how mutation–selection dynamics shape antibody evolution and may support model guided approaches to vaccine and immunotherapy design.

References:

1. Fowler DM, Fields S. Deep mutational scanning: a new style of protein science. *Nat Methods*. 2014;11(8):801-807. doi:10.1038/nmeth.3027
2. Schulz S, Tan TJC, Wu NC, Wang S. Epistatic hotspots organize antibody fitness landscape and boost evolvability. *Proc Natl Acad Sci USA*. 2025;122(2):e2413884122. doi:10.1073/pnas.2413884122
3. Adams RM, Kinney JB, Walczak AM, Mora T. Epistasis in a Fitness Landscape Defined by Antibody-Antigen Binding Free Energy. *Cell Syst*. 2019;8(1):86-93.e3. doi:10.1016/j.cels.2018.12.004
4. Schacht SS, Graffunder J, Durek P, et al. Activation and maturation of antigen-specific B cells in nonectopic lung infiltrates are independent of germinal center reactions in the draining lymph node. *Cell Mol Immunol.* 2025;22(6):612-627. doi:10.1038/s41423-025-01285-8

A covariation-based framework to model proteome network dynamics and phenotypic heterogeneity in Candida albicans

Luise Nagel[1], Savvas Kourtis[2], Austin Mottola[1], Georg Kustatscher[2], Markus Ralser[1,3,4]

[1]Department of Biochemistry, Charité-Universitätsmedizin Berlin, Berlin, Germany; [2]Centre for Cell Biology, University of Edinburgh, Edinburgh, UK; [3]Exploratory Diagnostic Sciences, Berlin Institute of Health at Charité, Berlin, Germany; [4]Max Planck Institute for Molecular Genetics, Berlin, Germany

Unraveling the mechanisms by which molecular networks give rise to phenotypic variation remains an ongoing challenge in the field of systems biology. The analysis of protein abundance covariation provides a quantitative framework for the inference of metabolic state-associated functional organisation, and facilitates the identification of phenotype-driven changes in signaling pathways. In this study, we present a large-scale quantitative proteomics dataset covering 95 Candida albicans strains, which have been profiled by mass spectrometry across eleven different conditions. We exploit covariation at two levels: (i) across the complete dataset to capture global co-regulation and increase functional protein annotation, and (ii) within each condition to resolve condition-specific network architectures and variation in the covariation of proteins. Using clustering of pairwise protein covariation, we characterize co-regulated protein modules that reflect metabolic and signaling organization. Next, we introduce a covariation stability score based on the variance of pairwise correlation coefficients between conditions. This metric highlights proteins whose network connectivity is either robust or markedly flexible, providing a quantitative measure of functional plasticity. Finally, we relate inter-strain phenotypic diversity to both differential protein abundance and alterations in covariation structure. The proposed framework establishes condition-resolved protein covariation analysis as a scalable approach to systematically annotating poorly characterized proteins, inferring functional proteome organization, and revealing network plasticity from population-level proteomics data under environmental perturbations.

Regulation of Notch signalling dynamics by cis-binding and cell neighborhood relationships.

Specioza Nambooze[1], Annah Naturinda[1], Nick Monk[1,2]

[1]African Institute for Mathematical Sciences (AIMS) Ghana, Ghana; [2]University of Sheffield, UK

The Notch signaling is involved in many developmental processes in which neighboring cells adopt distinct fates. Examples of such processes include proliferation and the formation of checkerboard like patterns of differentiation, as occurs during Drosophila bristle patterning. Lateral inhibition is a fundamental mechanism that amplifies small differences between neighboring cells into stable patterns of cell fate. The dynamics of lateral inhibition depend on how the signaling and feedback are set up, which determines whether the system exhibits oscillatory behavior or bistability. We analyze a Notch-Delta binding model where signaling is mediated primarily by trans interactions, and NICD represses Delta production via a negative feedback loop with an explicit time delay. Without delay the system undergoes a pitchfork bifurcation when the NICD-Delta regulation slope exceeds a critical threshold producing bistability. In this setting, the system does not display oscillatory dynamics and the spatially homogeneous mode remains linearly stable. Introducing the delay produces a critical delay in the spatially homogeneous mode where the system undergoes a Hopf bifurcation hence generating oscillations beyond that point. Adding cis interactions raises the pitchfork threshold and makes it more difficult to go through a Hopf bifurcation, thereby dampening oscillations and stabilizing pattern formation, a potential new role of cis binding. These results suggest that the binding model has a Hopf bifurcation if the delay in the feedback is strong enough and that cis binding suppresses these oscillations.

Unjustified Poisson assumptions lead to overconfident estimates of the effective reproductive number

Barbora Nemcová[1], Isaac Goldstein[2], Jessalyn Sebastian[3], Volodymyr Minin[3#], Johannes Bracher[1#]

[1]Karlsruhe Institute of Technology, Karlsruhe, Germany; [2]Stanford University, USA; [3]University of California, Irvine, USA

[#]shared last authorship

Time-varying effective reproductive numbers of infectious diseases are commonly estimated using renewal equation models. In the widely applied R package EpiEstim, this approach is combined with a Poisson distributional assumption. This has been criticized on various occasions, mostly on grounds of general model realism or a desire to estimate overdispersion parameters. We argue that an important issue arising from the Poisson assumption is that inference about the effective reproductive number becomes overconfident in presence of overdispersion. By how much standard errors are underestimated follows in a straightforward manner from theory on generalized linear models. We therefore recommend to replace the Poisson assumption by quasi-Poisson or negative binomial extensions, and contrast their respective properties. We illustrate our arguments in three examples on Ebola, pandemic influenza and COVID-19.

Understanding the Transmission and Spread of Drug Sensitive and Resistant Strains within a Population: A Mathematical Modelling Approach

Nicholas Opoku, Nicholas Monk

African Institute for Mathematical Sciences Ghana, Ghana

The global rise of antimicrobial resistance (AMR) presents a critical challenge to public health, threatening to reverse decades of progress in infectious disease control. While the biological mechanisms underpinning resistance are increasingly well characterized, the population-level dynamics governing the coexistence and competition of drug-sensitive and drug-resistant strains remain poorly understood. Our study develops and analyses a suite of deterministic mathematical models to elucidate the mechanisms driving the transmission, persistence, and potential dominance of resistant pathogens in heterogeneous host populations. Our framework integrates epidemiological compartments representing infection with sensitive and resistant strains incorporating realistic demographic and behavioral heterogeneities. The model explicitly captures key processes including differential transmissibility, fitness costs associated with resistance and imperfect adherence. Both analytical and numerical approaches are employed to investigate the system's equilibria, basic reproduction numbers (R_0), and invasion thresholds for resistant strains. Results reveal the existence of multiple stable equilibria suggesting the potential bistability, where small perturbations in transmission parameters tip the population toward dominance by resistant or sensitive strains. Sensitivity analyses identify the most influential parameters driving resistance spread thereby offering quantitative guidance for prioritizing control strategies. The results emphasize that resistance management requires not only prudent antibiotic use but also an understanding of the nonlinear feedbacks inherent in transmission systems. The approach presented here can be readily adapted to a range of pathogens, including bacterial, viral, and parasitic diseases, where resistance evolution poses a pressing threat. Ultimately, this modelling framework serves as a decision-support tool for designing sustainable intervention strategies that balance effective treatment of infections with the long-term containment of resistance within populations.

Bayesian Framework for Joint Motion-Compensated 3D MRI Reconstruction

Antonio de Jesus Ortiz Gonzalez[1], Alexander Effland[2], Erich Kobler[3], Lukas Schletter[4,5]

[1]Life & Medical Sciences Institut (LIMES), University of Bonn, Germany; [2]Institute for Applied Mathematics, University of Bonn, Germany; [3]Institute for Machine Learning, Johannes Kepler University Linz, Germany; [4]German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany; [5]University Hospital Bonn, Germany

Magnetic Resonance Imaging (MRI) is highly sensitive to patient motion, which disrupts k-space encoding and leads to blurring, ghosting, and loss of anatomical detail, especially in high-resolution 3D acquisitions. Most existing motion correction approaches rely on 2D slice-based processing, even though motion inherently occurs in three dimensions, causing residual artifacts and inter-slice inconsistencies. We propose a physics-consistent Bayesian framework for 3D motion-compensated MRI reconstruction that jointly estimates anatomical images, rigid-body motion, and coil sensitivity maps directly from undersampled, motion-corrupted k-space data. The formulation integrates three complementary priors: (i) a score-based diffusion prior serving as a powerful data-driven anatomical regularizer; (ii) a temporal smoothness prior enforcing physically plausible motion trajectories; and (iii) a Tikhonov–Laplacian coil prior promoting spatially smooth and well-scaled sensitivity maps. Inference alternates deterministic reverse-diffusion updates for image restoration with proximal optimization for motion and coil estimation, ensuring k-space consistency without paired supervision or external navigators. The resulting solver performs fully unsupervised reconstruction and generalizes across motion types and sampling patterns. Extensive experiments on both simulated and real 3D brain MRI datasets demonstrate that our proposed method significantly enhances motion artifact suppression and structural fidelity compared to existing k-space, image-space, and deep learning-based techniques. The approach is robust even under severe motion and high acceleration, successfully recovering fine anatomical details while maintaining realistic texture. These results suggest that combining diffusion-based anatomical priors with physics-guided joint estimation of motion and coil sensitivities can enable accurate, unsupervised motion compensation in 3D MRI. This represents a promising direction for clinically practical, high-fidelity 3D MRI reconstruction.

Benchmarking precision matrix estimation methods for differential co-expression network analysis

Matthias Overmann, Gordon Grabert, Tim Kacprowski

Institute of Data Science in Biomedicine, Technische Universität Braunschweig, Germany; Braunschweig Integrated Centre of Systems Biology (BRICS), Technische Universität Braunschweig, Germany

Gene expression profiling is widely used to investigate disease mechanisms, yet classical analyses such as differential expression or pairwise correlation analysis offer only limited interpretability. These approaches treat genes or gene pairs in isolation and fail to capture the complex dependency structure underlying molecular regulation. As a result, indirect effects, confounding relationships, and higher-order dependencies remain hidden. Network-based differential co-expression analysis addresses these limitations by modeling the entire system of gene–gene dependencies. This reveals condition-specific alterations in connectivity patterns rather than changes in individual genes or pairwise correlations alone. To separate direct from indirect associations, such networks can be based on partial correlations, which quantify the relationship between two variables while accounting for all others. These partial correlations are obtained from the inverse covariance, the precision matrix However, in gene expression profiling, the number of genes typically greatly exceeds the number of available samples, which makes exact calculation of precision matrices intractable. Instead we have to rely on computationally challenging estimation methods. Numerous precision matrix estimation methods (PMEMs), often based on sparse regularization, can be applied to this setting, yet their comparative performance under realistic data conditions remains unclear. We established a simulation framework to systematically assess their performance. It generates gene expression datasets with controllable and known ground-truth partial correlation structures. This enables quantitative benchmarking of a wide range of PMEMs across diverse simulation settings, including variations in covariance structure, precision matrix density, covariance strength, sample size–to–dimension ratios, and data distributions. We present an unbiased and reproducible basis for comparing estimation accuracy and stability. The analyses demonstrated that PMEMs are very sensitive to a multitude of data characteristics. Too narrow and selective assessment of PMEMs risks misleading, non-comparable and non-reproducible findings. Sparse estimators, e.g., directly impose structural constraints that promote interpretability. However, in this study, methods based on l_1 regularization often produced overly sparse networks and showed low differential edge recovery, which in real-world analyses may result in the loss of biologically meaningful connections. In contrast, the elastic net–based GLassoElnetFast consistently demonstrated superior accuracy in recovering differential edges across a wide range of simulation scenarios. Overall, the study emphasizes that results derived from limited benchmarks may not generalize. Our simulation framework enables a systematic and reproducible comparison of estimators, offering a basis for method development and standardized evaluation. Beyond benchmarking, the findings have broader implications for applied differential co-expression network analyses: the choice of estimator can strongly influence inferred network topology and, consequently, biological interpretation.

Groundwork for open-source nonlinear mixed-effects modeling and quantitative systems pharmacology, with SBML and Petab

Dilan Pathirana, Jonas Arruda, Jan Hasenauer

Life and Medical Sciences (LIMES) Institute, University of Bonn, Germany; Bonn Center for Mathematical Life Sciences, University of Bonn, Germany

Nonlinear mixed effects (NLME) and quantitative systems pharmacology (QSP) modeling enable individual-specific parameter inference and drug response prediction. Hence, these "population" approaches are used in the pharma industry to study drugs across demographics. However, popular tools are often costly, closed-source, or not interoperable, which limits their utility in research, especially for use cases outside of the pharma industry. To address this issue, we enable NLME and QSP in pre-existing systems biology workflows. In particular, we extend the PEtab (and thereby SBML) file format to specify individualized data and the fixed and random effects of NLME. We extend the Parameter Estimation Toolbox for Python (pyPESTO) with implementations of NLME methods, specifically the stochastic approximation of expectation-maximization (SAEM) and marginal likelihood approximations. This open-source framework enables modelers to implement their model once then assess the population, population-average, and individual approaches on several modeling tasks, including parameter estimation, uncertainty quantification and optimization of drug doses.

Modeling Vaccine-Induced Antibody Dynamics Using Nonlinear Mixed-Effects Models in Healthcare Workers

Clemens Peiter[1,2], Paolo Boffetta[3,4], Jan Hasenauer[1,2], ORCHESTRA WP5 Working Group

[1]Life and Medical Sciences Institute, Bonn University, Bonn, Germany; [2]Bonn Center for Mathematical Life Sciences, Bonn University, Bonn, Germany; [3]Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy; [4]Stony Brook Cancer Center, Stony Brooke University, Stony Brook, NY, USA

New virus strains of SARS-CoV-2 require ongoing protection against infection. An effective measure against infection is vaccination, which has been shown to provide strong protection against serious illness, hospitalization and death. However, the response to vaccination can differ widely between individuals and effects of different covariates on the dynamics of the response remain poorly explored. In this work, we employed a mathematical model describing the antibody response in individuals that were vaccinated against COVID-19. All reactions are expressed in a system of ordinary differential equations and the model is embedded in a nonlinear mixed-effects modeling framework to best capture the inter-individual heterogeneity. Most parameters of our model are unknown and need to be estimated from data, which was obtained from partners of the EU-funded project ORCHESTRA ("Connecting European Cohorts to Increase Common and Effective Response To SARS-CoV-2 Pandemic"). The data is used to calibrate our model, predict antibody responses after vaccination and analyze the effect of different covariates on the dynamics of the antibody response. Thus, we provide a model that allows us to explain inter-individual heterogeneities that affect the dynamics of antibody titers and identify important factors influencing the immune response.

Mapping Lesion Niches: How Microglia Adapt to Recurrent Demyelination

Katrin Perez Anderson

University Hospital Bonn, Germany; DZNE, Bonn, Germany

While most neurodegenerative disease, such as Alzheimer's disease or Parkinson's disease occur in higher age with protein aggregates accumulating, disrupting and destroying neurons, the way how multiple sclerosis (MS) destroys neurons seems to differ at first glance. In MS the immune system is reactive towards myelin – the isolation layer wrapping around neuronal axons - which makes inflammation a predominant feature in MS pathology. However, inflammation has been shown to be a common feature in all neurodegenerative diseases, with the tissue resident macrophages of the brain – microglia – playing a critical role in protection as well as destruction of neurons. To study how repeated inflammation shifts cellular dynamics in the brain, in a unique approach, we challenged murine brains by sequentially and stereotactically injecting lysolecithin, a demyelinating agent, that in the early stage causes vast demyelination, characterized by the infiltration of myeloid cells. In later stages, demyelination by oligodendrocyte precursor cells (OPCs) occurs. In our sequential injection model, we inject lysolecithin up to three times in the same white matter region during the late demyelination phase, to mimic a relapsing demyelination attack, similar as in relapsing-remitting MS. We analyzed single cell RNA sequencing, as well as spatial transcriptomics ST data, to capture transcriptional programs shifting microglia identities. We could identify a cell population that seems to act as a hub and catalyst for the development into disease-associated microglial subtypes, giving us deeper insights into cellular dynamics. Understanding these microglial dynamics paves the way to study intervention points and ultimately to develop pharmacological approaches with the hope to alleviate patient's disease burden. As these principles could apply to not only demyelinating diseases such as MS, these foundational insights might benefit not only MS patients, but all neurodegenerative diseases.

Incorporating tumor growth models into physical simulation of radiological, nuclear medicine, and optical imaging systems

Jörg Peter, Dhritman Dhar, Mark Ladd

German Cancer Research Center (DKFZ), Heidelberg, Germany

This research project aims to integrate and extend boundary-driven tumor growth models, commonly utilized by cancer biologists, into physical simulation frameworks for the study of radiological imaging modalities such as x-ray computed tomography (CT) and magnetic resonance imaging (MRI), nuclear medicine techniques including single-photon emission computed tomography (SPECT) and positron emission tomography (PET), as well as optical imaging technologies such as bioluminescence imaging (BLI) and fluorescence imaging (FMI). The proposed methodology establishes a software-based workflow that manages and integrates tumor growth modeling, physical image simulation, and tomographic image reconstruction for both single- and multimodal biomedical imaging applications. Particle-based image simulation is conducted using statistical estimates of Boltzmann transport within heterogeneous phantom and tumor cell geometries. Spatially selective magnetic resonance signals are simulated in Liouville space by applying the Liouville–von Neumann equation, and imaging simulation is achieved by depositing radio-frequency energy at discrete k-space locations. Tomography is performed within particle-based simulations, employing advanced iterative image reconstruction algorithms. A central aspect of this research is the incorporation of tumor clouds and their associated biological and physical parameters, including dynamic source definitions, into the geometric modeling of anthropomorphic and animal phantoms. Geometric complexity ranges from simple quadrics to hybrid mesh-based phantom descriptions. Multiple modeling strategies for tumor development are implemented using three-dimensional lattices, encompassing discrete, continuous, and hybrid model formalisms. Tumor growth is formulated as cell clouds following the Eden growth model, where cells compete with their nearest neighbors and interact according to defined rules. This process can occur prior to imaging or be fully integrated into a temporal imaging sequence, enabling the in vivo imaging of single-cell genetic or epigenetic mutations at single-cell resolution, and extending to the formation of large cancer clusters comprising billions of cells and potentially multiple metastatic sites in probabilistically selected tissues. The framework is designed to support biologists in investigating the evolutionary processes and genetic signatures underlying tumor progression, while also facilitating fully simulated in vivo preclinical and clinical imaging scenarios. A primary advantage of this approach is the complete a priori knowledge of the phantom or anatomical context, including the genetic signature of the evolving tumor and the source distribution, particularly when simulating particle-based molecular-genetic imaging such as BLI and PET. Although this framework enables a range of research investigations, such as the study of pharmacokinetic models in tumor cell clouds as performed in nuclear medicine imaging, a key question concerns the minimum number of cell alterations required for detectability in reconstructed images of any modality. This question is complex and depends on multiple parameters throughout the simulation framework. Currently, tumor cells invade specific tissues based on the self-sufficient model selected, forming invasive tumor masses. Building upon the baseline model, the Eden growth process is additionally governed by the spatial arrangement of phantom tissues through which the tumor advances. The effects of mechanical forces or growth-induced solid stress on tumor proliferation across phantom tissue boundaries have not yet been implemented and will be addressed in future research.

Modelling the HPA axis: Mechanisms and individual variability in a human cohort

Maren Philipps[1,2], Thomas J. Upton[3], Stafford L. Lightman[3], Jan Hasenauer[1,2], Eder Zavala[4]

[1]Life & Medical Sciences Institute (LIMES), University of Bonn, Bonn, Germany; [2]Bonn Center for Mathematical Life Sciences, University of Bonn, Bonn, Germany; [3]Henry Wellcome Laboratories for Integrative Neuroscience and Endocrinology, Translational Health Sciences, Faculty of Health Sciences, University of Bristol, UK; [4]Centre for Systems Modelling and Quantitative Biomedicine, University of Birmingham, Edgbaston, UK

The endocrine stress response is mediated by the hypothalamus-pituitary-adrenal (HPA) axis, where circadian, physiological and cognitive inputs are integrated at the hypothalamus to drive the release of adrenal hormones such as cortisol. These hormones regulate a symphony of metabolic and physiological processes, ranging from the immune response to the mental state. However, despite its critical role in human health and behaviour, the underlying regulatory mechanisms of the HPA axis remain incompletely understood, partly due to the substantial inter- and intra-individual variability and the fast ultradian fluctuations in hormone levels. Upton, Zavala et al. have generated a high-resolution data set of hormones related to the HPA axis in a cohort of 214 healthy individuals, spearheading a novel, less invasive sampling technique from interstitial fluid (ISF).1 Building on this dataset, we develop mechanistic models to investigate how systemic hormone concentrations give rise to tissue-specific effects. Our models identify the biological mechanisms that best explain the dynamics of cortisol and cortisone in blood and ISF in healthy individuals. We further assess how the enzyme-mediated inter-conversion between cortisol and cortisone modulates the availability of active cortisol dependent on the time of day. Ultimately, this framework helps pinpoint the most relevant individual-specific effects, thereby characterising the drivers of heterogeneity in healthy endocrine function.

1. Upton TJ, Zavala E, Methlie P, et al. High-resolution daily profiles of tissue adrenal steroids by portable automated collection. *Sci Transl Med*. 2023;15(701):eadg8464. doi:10.1126/scitranslmed.adg8464

Mathematical modelling of electroporation

Lorena Pohl, Barbara Niethammer, Juan Velázquez

University of Bonn, Germany

Electroporation is a widely applied technique to introduce DNA or other molecules into biological cells by briefly increasing the permeability of their cell membrane. To this end, the cells are exposed to high-voltage electric pulses, which transiently increases the transmembrane potential. When a certain threshold value is reached, membrane permeability rapidly and significantly increases. Depending on the circumstances, the membrane may breakdown (irreversible electroporation) or recover after removal of the electrical field (reversible electroporation). One mechanism underlying this phenomenom is the formation and resealing of nanoscale hydrophilic pores due to the increased transmembrane potential. The small size and insufficient stability of the pores has thus far prevented the visualization of their dynamics via microscopy, calling for mathematical modelling and analysis to bridge the gap. We present a model coupling pore formation and growth with the effect of large pores on the transmembrane potential, where the membrane is modelled as a combination of a conductor and a capacitator. We describe simplifications of the model for a bilayer lipid membrane and scaling limits depending on the timescale of the applied electric pulses and the shape of the pore energy, and examine their differing behaviour.

In silico and patient-derived organoid-based therapy recommendations for colon carcinomas

Sneha Pushpa Ramesan[1], Marieta Toma[2], Tim Vilz[3], Nils Sommer[3], Verena Tischler[2], Elena S. Reckzeh[1]

[1]TRA Life & Health, LIMES-Institute, University of Bonn, Germany; [2]Institute of Pathology, University Hospital Bonn, Germany; [3]Clinic and Polyclinic for General, Visceral, Thoracic and Vascular Surgery, University Hospital Bonn, Germany

Colorectal cancer (CRC) is the second leading cause of cancer-related mortality worldwide, accounting for 930,000 deaths in 2020.[1] Traditional pre-clinical models such as 2D cell line and patient-derived tumor xenografts (PDTX) often fail in replicating promising therapies in clinical trials. Patient-derived organoids (PDOs) are a useful model that potentially bridges this gap. These three-dimensional cell cultures reproduce the genetic and phenotypic characteristics of the original tumours and provide a physiologically relevant platform for drug testing and the development of personalized therapies. In collaboration with the University Hospital Bonn, Prof. Dr. Jan Hasenauer and EsqLabs, this project aims to develop a platform, that integrates computational modelling and experimental organoid systems to improve the quality of life and treatment outcomes of colon cancer patients. Tumor resections (including tumor, metastasis, and normal tissue) from 40 colorectal cancer patients will be used to establish an organoid biobank. The data from molecular characterization of these samples through whole exome sequencing (WES) and transcriptomic analysis will be used for the prediction of the most effective drugs and drug combinations using computational models. Followed by drug screening, final predictions will be validated in a non-interventional study, contributing to the establishment of a robust drug prediction pipeline for colorectal cancer. Protocols for generating patient-derived organoid lines have been successfully established. Preliminary characterization confirmed that the organoid model effectively recapitulates key features of primary tumors, providing a robust system for downstream experiments.

Reference:

1. Siegel RL, Wagle NS, Cercek A, Smith RA, Jemal A. Colorectal cancer statistics, 2023. *CA Cancer J Clin*. 2023;73(3):233-254. doi:10.3322/caac.21772

Prediction of Drug Response in Patient-derived Organoids using Large-Scale Mechanistic Models

Moritz Richter, Dilan Pathirana, Jan Hasenauer

Computational Biology, Life & Medical Sciences (LIMES) Institute, University of Bonn, Germany; Bonn Center of Mathematical Life Sciences, University of Bonn, Germany

Mathematical modeling of cellular signaling pathways has the potential to aid in the search for optimal, individualized therapies for patients. Here, we present an approach to evaluate drug effectiveness for treating colorectal cancer. This approach is based on a mechanistic ordinary differential equation (ODE) system consisting of over 2,000 reactions and more than 1,000 species. This system reflects some of the most relevant cancer-associated signaling pathways. We use sequencing data from patient biopsies to individualize the model and test our predictions against cell viability data generated from patient-derived organoids.

Modeling vertical HIV transmission: a comparison with WHO high-risk assessment in the LIFE studies

Sandra Rjeschni[1], Kira Elsbernd[1], Bindiya Meggi[2], Anange Fred Lwilla[3], Ilesh V. Jani[2], Issa Sabi[3], Noemi Castelletti[1,4,5], Arne Kroidl[1], LIFE Study Consortium

[1]Institute of Infectious Diseases and Tropical Medicine, LMU University Hospital, LMU Munich, Munich, Germany; [2]Instituto Nacional da Saúde, Marracuene, Mozambique; [3]National Institute for Medical Research, Mbeya Medical Research Center, Mbeya, Tanzania; [4]Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology, Infection and Pandemic Research, Munich, Germany; [5]Institute of Radiation Medicine, Helmholtz Zentrum München, Neuherberg, Germany

Background Vertical HIV transmission has declined worldwide, yet an estimated 120,000 children still acquired HIV in 2023, particularly in sub-Saharan Africa, due to gaps in antenatal care, antiretroviral treatment (ART) access, and maternal viral suppression. The current WHO high-risk classification criteria for vertical transmission, based on a limited set of maternal factors (new HIV diagnosis at delivery, recent high viral load, lack of ART or short ART exposure), may underestimate risk. Method We developed a data-driven model to predict vertical HIV transmission using data from the LIFE (Long-term Impact on inFant hEalth) cluster-randomized controlled trial. The study was conducted at 28 health facilities in Tanzania between October 2019 and January 2023 and included 6,580 infants followed for at least 12 weeks from birth. Among them, 137 infants acquired HIV. For additional testing, data from the ongoing stepped-wedge cluster-randomized study LIFE2Scale (N=3834, transmissions=40), conducted in the same regions, were used, with participants enrolled over a 14-week period. Candidate models included CatBoost (gradient boosting decision trees) and penalized logistic regression. During tuning, CatBoost consistently selected a maximum tree depth of 1, indicating mainly additive effects. Consequently, we adopted a weighted logistic regression with elastic net regularization (R package glmnet) for interpretability. The LIFE study data set was split into training (70%) and testing (30%) subsets, stratified by transmission status to preserve class proportions. Missing data were imputed using k-nearest neighbors ($k = 5$), fitted on the training set, and applied to the test set. Model hyperparameters (regularization strength λ, mixing parameter α, and decision threshold) were optimized using stratified 3-fold cross-validation based on the F-β score ($\beta = 6$). Class imbalance was addressed by applying class weights inversely proportional to class prevalence. The final model was evaluated on the LIFE study test set and additionally on the LIFE2Scale data set to assess translatability. Model performance was compared with the WHO high-risk criteria calculated for the same data sets. Results On the independent test set (N=1974) from the LIFE study, the model achieved a sensitivity of 81.1% vs. WHO 59.5%, while almost maintaining specificity (83.3% vs. WHO 89.4%) and precision (8.5% vs. WHO 9.7%). The PR-AUC was 0.15 and the ROC-AUC was 0.87. The model correctly identified 30 out of 37 infants acquiring HIV in this set. The predictors of transmission selected by the model were (ordered by importance) maternal viral load, infant weight, country, and maternal age at delivery. Hyperparameter tuning selected $\alpha = 0.1$, $\lambda = 0.4$, and a decision threshold of 0.68. The results for the LIFE2Scale dataset were as follows: sensitivity – GLM: 72.5%, WHO: 72.5%; specificity – GLM: 90.6%, WHO: 87.8%; precision – GLM: 7.5%, WHO: 5.9%. Conclusion and Outlook Our penalized logistic regression model achieved higher sensitivity than the WHO risk criteria while maintaining comparable specificity, highlighting the potential of data-driven risk assessment to improve the identification of infants at high risk of HIV acquisition. Reduced sensitivity in the external dataset, relative to the internal evaluation, demonstrates challenges in model generalizability across temporal and implementation contexts. Additional ongoing work focuses on evaluating alternative imputation strategies to strengthen model robustness when data, especially maternal viral load, is unavailable.

Glucose Uptake Assay to Study Functional Maturation of Intestinal Organoids

Annika Rohde, Dirk J. Mastebroek, Melanie Thielisch, Elena S. Reckzeh

TRA Life & Health, LIMES-Institute, University of Bonn, Germany

Glucose enters cells via two transporter families: passive GLUTs and active SGLTs. These days SGLT1 and SGLT2 are getting more in focus as therapeutic targets especially for diabetes. To test potential drugs, a reliable glucose uptake assay is needed. Traditionally, radioactive glucose analogues like ^{14}C-AMG are used in glucose uptake assays but these have safety and cost drawbacks. The fluorescent probe 1-(N-(7-Nitrobenz-2-oxa-1,3-diazol-4-yl) amino)-1-deoxy-d-glucose (1-NBDG), unlike 2-NBDG, is transported by both GLUTs and SGLTs and remains stable under alkaline conditions, enabling simpler, safer assays. Using human SGLT1- and SGLT2-expressing cell lines, researchers developed and validated a high-throughput screening method with 1-NBDG, showing results consistent with traditional radioactive assays. In this Project, self-synthesized 1-NBDG is used to set up a functional glucose uptake assay in human small intestinal organoids. The assay is validated using known SGLT1 inhibitors with either an image based or a spectrophotometric readout. When testing different differentiation conditions, a disconnection between the results gained during functional testing with the 1-NBDG assay and gene expression levels were discovered. This result highlights the need for a reliable functional glucose assay in addition to RT-qPCR for drug discovery and basic research.

BaCoN (Balanced Correlation Network) improves prediction of gene buffering

Thomas Rohde[1], Talip Yasir Demirtas[1], Angela Helen Shaw[1], Maximilian Billmann[1], Sebastian Süsser[2], Manuel Kaulich[2]

[1]Institute of Human Genetics, University Hospital Bonn, Germany; [2]Institute of Biochemistry II, Faculty of Medicine, Goethe University Frankfurt, Germany

Buffering between genes, where one gene can compensate for the loss of another gene, is fundamental for robust cellular functions. While experimentally testing all possible gene pairs is infeasible, gene buffering can be predicted genome-wide under the assumption that a gene's buffering capacity depends on its expression level and its absence primes a severe fitness phenotype of the buffered gene. We developed BaCoN (Balanced Correlation Network), a post hoc unsupervised correction method that amplifies specific signals in expression-vs-fitness correlation networks. We quantified 147 million potential buffering relationships by associating CRISPR-Cas9-screening fitness effects with transcriptomic data across 1019 Cancer Dependency Map (DepMap) cell lines. BaCoN outperformed state-of-the-art methods, including multiple linear regression based on our compiled gene buffering prediction metrics. Combining BaCoN with batch correction or Cholesky data whitening further boosts predictive performance. We characterized 808 high-confidence buffering predictions and found that in contrast to buffering gene pairs overall, buffering paralogs were on different chromosomes. BaCoN performance increases with more screens and genes considered, making it a valuable tool for gene buffering predictions from the growing DepMap.

Modelling pattern formation in spatially discrete systems

Patience Aba Sakyi[1], Nicholas Alexander Miles Monk[1,2]

[1]African Institute for Mathematical Sciences Ghana, Ghana; [2]University of Sheffield, UK

A fundamental process that lies at the heart of the development of living systems is the formation of complex patterns from a uniformly homogeneous start point. Biological pattern formation is often based on non-linear interactions of chemicals and their movement, and reaction-diffusion models are a classic theoretical framework for explaining such patterning. A good example of such patterning is seen in the root of Arabidopsis thaliana, where each cell commits to one of two fates: hair cell and non-hair cell. Experimental data reveal a puzzling phenomenon in this system: two core factors in the regulatory network (GL3 and CPC) are predominantly transcribed in one cell type but their proteins accumulate in the opposite cell type – a counter-intuitive observation that challenges classical reaction-diffusion models like the ones based on local-activation lateral-inhibition (LALI). The same gene regulatory network used in root hair patterning operates in leaf hair patterning, primarily via homologous proteins. Notably, while root hair cells arise in regions with low levels of the WER-GL3 complex, leaf hair cells (trichomes) form in regions with high levels of the corresponding complex. These observations raise fundamental questions about how cellular networks achieve robust and flexible spatial organisation and how evolutionarily conserved networks dynamically select context-dependent regulatory logic to produce diverse, tissue-specific outcomes. In this work, we use the mutual support model by Savage et al. (2008) as a framework to study a spatially discrete reaction-diffusion system in which proteins move between neighbouring cells through plasmodesmata rather than by extracellular diffusion. The model captures a distinctive feature of this system: proteins form immobile complexes acting as sinks, thereby influencing intercellular distribution. Unlike classical activator-inhibitor systems, there is no obvious local activation, raising new questions about the regulatory setup that allows patterned cell fate decisions. We investigate how these properties allow the network to generate and maintain stable spatial patterns and consider how factors such as positional cues or directional transport might further refine pattern selection.

Enhancing Clinical Immunology and Disease Diagnostics with Global Swarm Learning

Ivan Savchuk[1]*, Stefanie Warnat-Herresthal[1,2]*, Lucas Secchim Ribeiro[1], Benedikt Clemens[1], Kilian Dahm[1], Johanne Elsner[1,2], Lisa Holsten[1,2], Hartmut Schultze[1,3], Lorenzo Bonaguro[1,2], Maren Büttner[4], Matthias Becker[1], Global Swarm Learning Group, Anna Aschenbrenner[1,2#], Joachim L. Schultze[1,2#]

[1]Systems Medicine, Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE), Bonn, Germany; [2]Genomics and Immunoregulation, Life & Medical Sciences (LIMES) Institute, University of Bonn, Bonn, Germany; [3]Hewlett Packard Enterprise, Houston, Texas, USA; [4]Calico Life Sciences, San Francisco, California, USA

*shared first authorship; [#]shared last authorship

High-dimensional cytometry (HDC) has transformed human immunology, enabling the study of health and disease at single-cell granularity. Especially during the COVID-19 pandemic, HDC with specialized panels drove new disease understanding. However, cytometry data's heterogeneity limits its potential for clinical machine learning (ML). The large variety of platforms, instruments, and experimental settings introduces batch effects; low marker panel overlap renders many datasets incompatible; and data privacy regulations and technical barriers to large data transfer make data pooling difficult. Earlier, we proposed Swarm Learning as a democratic ML framework that overcomes limitations of local ML training while providing full data confidentiality. Here, we show how Swarm Learning can be applied to heterogeneous HDC data. We established a Global Swarm Learning Network for COVID-19 prediction, connecting 14 leading immunology institutions with data totaling 6,182 samples from 1,223 donors, combining different marker panels, technologies and COVID-19 disease states. We mapped all data to a common data model, developing a standardized pipeline for analysis, annotation and quality assessment. We replicated major biological findings across independent sites, such as reduced T-cell frequencies in patients with severe COVID-19. In the disease prediction setting, local models can achieve high performance when trained and tested on samples from the same site, but do not generalize across datasets from other sites; only models trained on diverse and sufficiently standardized data show broad generalization. Analysis of the common markers driving performance revealed the contribution of the T cell and monocyte compartments to disease prediction. In summary, this study highlights the potential of Swarm Learning to enable global collaboration, accelerate data harmonization and standardization efforts, and support a path towards ML-based clinical disease diagnostics.

Simulation-Based Inference of Realistic Intracellular Dynamics in Tissue-Scale CPMs through GPU Parallelization

Jan Dennis Schering, Johannes Textor

Radboud University, Nijmegen, The Netherlands

Motivation: In the life sciences, in-silico approaches complement traditional studies, addressing in vitro limitations which can be difficult and costly to set up and reproduce.[1-3] Within Cell Biology, the Cellular Potts Model (CPM) offers a complementary and reproducible tool for spatial simulations of dynamic intracellular behavior over time.[2,4] Due to its flexible, modular nature, the CPM has been applied to study a large variety of phenomena, including immune cell recruitment, migration and the study of tumor growth.[5,6] However, two bottlenecks limit the application of the CPM to large scale, physiologically realistic studies. First, the simulation time of the CPM is dependent on the size of the simulated space, growing quadratically in cost for 2D simulations and cubically for 3D.[2] Second, the parameters of the CPM lack biophysical correlates. Instead, methods are required to fit the model parameters to experimental data. As the CPM does not have a defined likelihood function, this requires generating a large amount of samples from the model, which is currently prohibitively slow.[1,2] One way to address the computational limitations of the model is through usage of modern GPU processing. In [2], our group used a checkerboarding scheme to speed up CPM simulations by several orders of magnitude, showcasing the immense potential of this approach, while highlighting existing limitations. That is, the checkerboarding can drastically alter the local update statistics of the CPM. In the worst case, this leads to a failure in reproducing phenomena of interest and needs to be carefully tuned. Results: Building on our previous work in [2], we introduce a new parallelization scheme of the CPM tailored towards GPUs. The new scheme significantly improves preservation of the local update statistics of the standard CPM, while showing similar performance to the checkerboarding and significantly reducing overhead. We have implemented this new scheme by building on a modern non-tensor GPU interface introduced in [8] to provide an easy to use-and-extend Python package available under [A]. Researchers can easily move their own CPM models to this implementation. To demonstrate this, we have re-implemented several established CPMs in 2D and 3D, including models for differential cell sorting, cell migration and tumor growth.[4,9,10] The package comes with an R interface, available under [B]. Further, we address the issue of parameter fitting by enabling parallelization of the simulations on a batch level, allowing for thousands of simulations to run at the same time. Using an example dataset of immune cell migration,[7] we have combined the parallel CPM with methods from Sampling-based Inference[1] in order to fully automatically fit the parameters of a CPM, such that the cell dynamics replicate the migration patterns of various immune cells including T Cells and Neutrophils. To further validate this approach, we are currently fitting the parameters to various target data including tumor growth and infiltration. Future Work: We will build on the methods developed here to study immunodynamics at tissue scale. Using large-scale GPU clusters, we can potentially simulate up to $1cm^3$, a full lymph node, which can bring previously inaccessible insights to e.g. immunotherapy and tumor studies.

1. Cranmer K, Brehmer J, Louppe G. The frontier of simulation-based inference. *Proc Natl Acad Sci USA*. 2020;117(48):30055-30062. doi:10.1073/pnas.1912789117
2. Sultan S, Devi S, Mueller SN, Textor J. A parallelized cellular Potts model that enables simulations at tissue scale. arXiv. 2023. doi:10.48550/arXiv.2312.09317
3. Mittal R, Ho A, Adivikolanu H, et al. Exploring the potential of computer simulation models in drug testing and biomedical research: a systematic review. *Front Pharmacol*. 2025;16:1644907. doi:10.3389/fphar.2025.1644907
4. Graner F, Glazier JA. Simulation of biological cell sorting using a two-dimensional extended Potts model. *Phys Rev Lett*. 1992;69(13):2013-2016. doi:10.1103/PhysRevLett.69.2013
5. Szabó A, Merks RM. Cellular potts modeling of tumor growth, tumor invasion, and tumor evolution. *Front Oncol.* 2013;3:87. doi:10.3389/fonc.2013.00087
6. Wortel IMN, Postat J, Mihaylova M et al. Cooperative motility emerges in crowds of T cells but not neutrophils. bioRxiv. 2024. doi:10.1101/2024.10.21.618803

7. Wortel IMN, Liu AY, Dannenberg K, Berry JC, Miller MJ, Textor J. CelltrackR: An R package for fast and flexible analysis of immune cell migration data. *Immunoinformatics*. 2021;1-2:100003. doi:10.1016/j.immuno.2021.100003
8. Hu Y, Li TM, Anderson L, Ragan-Kelley J, Durand F. Taichi: a language for high-performance computation on spatially sparse data structures. *ACM Trans. Graph*. 2019;38(6):201. doi:10.1145/3355089.3356506
9. Niculescu I, Textor J, de Boer RJ. Crawling and Gliding: A Computational Model for Shape-Driven Cell Migration. *PLoS Comput Biol*. 2015;11(10):e1004280. doi:10.1371/journal.pcbi.1004280
10. Wortel IM, Textor J. Artistoo, a library to build, share, and explore simulations of cells and tissues in the web browser. *eLife*. 2021;10:e61288. doi:10.7554/eLife.61288

[A] https://shorturl.at/l2mJA
[B] https://shorturl.at/lXKMa

Universal differential equations for wastewater-based epidemiology

Nina Schmid[1,2], Nicole Zacharias[3], Christoph Höser[3], Johannes Bracher[4,5], Cihan Papan[3], Nico Mutters[3], Jan Hasenauer[1,2]

[1]Life & Medical Sciences Institute (LIMES), University of Bonn, Bonn, Germany; [2]Bonn Center for Mathematical Life Sciences, University of Bonn, Bonn, Germany; [3]Institute for Hygiene and Public Health, University Hospital Bonn, Bonn, Germany; [4]Institute of Statistics, Karlsruhe Institute of Technology, Karlsruhe, Germany; [5]Computational Statistics Group, Heidelberg Institute for Theoretical Studies, Heidelberg, Germany

Wastewater-based epidemiology provides a low-cost, scalable view of community infection dynamics, but converting these signals into actionable epidemiological quantities remains difficult. Mechanistic models offer interpretability. Yet, standard assumptions like a constant transmission rate limit realism over long simulation horizons and heterogeneous settings. We present a susceptible–exposed–infectious–recovered (SEIR) universal differential equation (UDE) that links wastewater viral loads to case counts, and embeds neural networks to represent time-varying parameters. Utilizing ensembles it quantifies uncertainty and identifiability. Applied to COVID-19 data from Bonn (Germany), it produces plausible out-of-sample projections of case counts over an up to 50-week reconstruction horizon; across five cities in Rhineland-Palatinate, it learns city-specific mappings to prevalence that generalise within each locale; and on an influenza dataset from Bonn, it transfers beyond SARS-CoV-2, indicating cross-pathogen portability. Compared to SEIR models with fixed transmission, the UDE captures non-stationary drivers (policy, behaviour, seasonality) without sacrificing epidemiological structure, while propagating observation and model uncertainty into the projections. More broadly, this framework provides a flexible basis for integrative infectious-disease modelling, in which additional data modalities (e.g., mobility, clinical testing, meteorological covariates) can inform the learned components to improve interpretability and calibration.

A mathematical framework for quantifying T cell expansion in acute and chronic regulatory contexts

Joanna Schnorr, Kevin Thurley

Biomathematics Division, Institute of Experimental Oncology, University Hospital Bonn, Germany

A fast and pathogen-specific supply of effector T cells is essential in the mammalian immune response to acute and chronic infections, as well as cancer.[1] While the basic principles of T cell activation and differentiation are well established, the mechanisms that control the balance between proliferation and differentiation remain incompletely understood. Building on a previous analysis on T helper cells,[2] we developed a mechanistic cell-circuit model, where T cell fate decisions – proliferation and differentiation or death – are governed by competing waiting times. These were modeled using exponential or Gamma distributions, where the latter represent response-time distributions that effectively capture transition delays without explicitly modeling intracellular mechanisms. Our analysis revealed that simple motifs where proliferation competes against differentiation are intrinsically unstable: As soon as the proliferation rate exceeds the differentiation rate, cell numbers tend to infinity, making controlled expansion impossible. We therefore introduced regulatory mechanisms involving cytokine-mediated feedback, such as IL-2 enhancement and antigen control of the proliferation, that stabilize cell numbers and generate realistic effector responses. We systematically compared the proliferative potential and efficiency of several acute motifs, varying in the number of proliferating precursor states and their regulation mechanisms. In the chronic scenario, where antigen is constant, additional regulation involving IL-10 inhibition of proliferation is required. We introduced exhausted cells and analyzed the chronicity of linear, early-branching, and late-branching motifs. Our framework provides a quantitative foundation for exploring how T cell population dynamics are shaped by circuit-level regulation, offering insights into immune responses during acute and chronic infections.

1. Steinheuer LM, Klümper N, Bald T, Thurley K. Untangling cell–cell communication networks and on-treatment response in immunotherapy. *Curr Opin Syst Biol*. 2025;40: 100534. doi:10.1016/j.coisb.2024.100534
2. Burt P, Thurley K. Distribution modeling quantifies collective T_H cell decision circuits in chronic inflammation. *Sci Adv*. 2023;9(37):eadg7668. doi:10.1126/sciadv.adg7668

Predicting T cell motility from a single image

Koert Schreurs[1], Aysha Cerf[2,3], Judith N. Mandl[2,3,4], Johannes Textor[1,5], Inge M. N. Wortel[1]

[1]Data Science, Institute for Computing and Information Sciences, Radboud University, Nijmegen, The Netherlands; [2]Department of Microbiology and Immunology, McGill University, Montréal, QC, Canada; [3]McGill Research Centre for Complex Traits, McGill University, Montréal, QC, Canada; [4]Department of Physiology, McGill University, Montréal, QC, Canada; [5]Medical BioSciences, Radboud University Medical Center, Nijmegen, The Netherlands

MOTIVATION Immune cells are constantly patrolling the body, moving through tissues to detect and respond to infections or diseases. Over the past decades, advances in microscopy and live-cell imaging have allowed us to observe immune cells in motion in living tissues in experimental settings, revealing the importance of cell motility in shaping immune responses. However, in clinical settings we do not have the luxury of observing immune cells in motion. For example, when we take biopsy samples to study immune cells infiltrates in tumors, cells are fixed to preserve the tissue, providing only a snapshot of the dynamics frozen in time. This raises the question of whether, and to what extent, a cell's movement can be predicted from a single snapshot. METHODS In this study we try to answer this question using snapshots derived from time-lapse widefield mi- croscopy data. Specifically, we use a dataset from previous work where T cells migrate in microchannels with various widths (6-30µm).[1] Importantly, for these videos high quality manually annotated tracks are available such that the migration dynamics underlying the snapshots are known. From these videos, we derived velocity vectors and corresponding snapshots which we use to train a convolutional neural network to predict a cell's veloc- ity using a single snapshot. The network was trained to minimize the mean squared error between the predicted and target velocities. RESULTS In the simplest case of individual cells migrating in the narrowest microchannels, where movement is essentially one-dimensional, our model successfully predicts the direction of moving cells with 85% accuracy, and can distinguish whether a cell is moving with 68% accuracy, demonstrating that snapshot images contain usable information about cell motility. Using an ablation study, we assessed which features, such as morphology and actin distribution, are essential for accurate predictions. We then extended the approach to cells migrating in groups and in wider channels that allow two-dimensional movement. Cells moving in a group were easier to predict than isolated cells and training on both types together improved performance, achieving 95% accuracy in predicting the direction of moving cells and a 79% accuracy for distinguishing moving versus non-moving. Predicting cells moving in two dimensions was harder, with the accuracy of distinguishing moving cells dropping to 73% and an average angle error of 39° for moving cells. To assess whether the model's predictions are accurate enough to derive meaningful information about the underlying cell dynamics in practice, we designed two experiments. First we evaluated our model on cells with a Dock8 knockout mutation, which is known to alter the actin distribution and increase migration speeds.[2] Using only snapshot images, the model correctly predicted these cells as moving faster on average, despite never having seen cells with Dock8 knockout before. In a second experiment, we tested whether the models predictions are sufficiently accurate to detect directed migration (taxis) from snapshot of a population of cells. We simulated taxis using a particle-based model and sampled snapshots of cells to match the distributions of speeds and angles in the taxis simulation. We then investigate how strong the taxis needs to be, and how many cells must be included in a snapshot, for our model's predictions to reliably detect directed migration. DISCUSSION Our results provide a proof of principle that snapshots can contain usable information about cell motility, suggesting that future studies could explore how much of this information is preserved in static imaging modalities, such as immunohistochemistry.

1. Wortel IMN, Postat J, Mihaylova M, et al. Cooperative motility emerges in crowds of T cells but not neutrophils. bioRxiv. 2024. doi:10.1101/2024.10.21.618803
2. Shen C, Cerf A, Postat J, et al. A Dock8-dependent mechanosensitive central actin pool maintains T cell shape and protects the nucleus during migration. *Sci Immunol*. 2025;10(109):eadt9239. doi:10.1126/sciimmunol.adt9239

Decoding Kupffer Cell Programming in Maternal Obesity-induced Fatty Liver via Integrated Multi-Omics and Functional Analysis

Lea Seep[1,2], Hao Huang[3]*, Nora R. Balzer[3]*, Iva Splichalova[3], Nelli Blank-Stein[3], Maria Francesca Viola[3], Eliana Franco Taveras[3], Kerim Acil[3], Diana Fink[3], Franzisca Petrovic[3], Nikola Makdissi[3], Seyhmus Bayar[3], Katharina Mauel[3], Carolin Radwaniak[3], Jelena Zurkovic[4], Amir H. Kayvanjoo[3], Klaus Wunderling[4], Malin Jessen[3], Mohamed H. Yaghmour[4], Lukas Kenner[5,6,7,8,9,10], Thomas Ulas[11,12,13], Stephan Grein[1,2], Joachim L. Schultze[11,12,13], Charlotte L. Scott[14,15], Martin Guilliams[16,17], Zhaoyuan Liu[18], Florent Ginhoux[18,19,20,21], Marc D. Beyer[11,13,22], Christoph Thiele[4], Felix Meissner[23], Jan Hasenauer[1,2], Dagmar Wachten[24], Elvira Mass[3]

[1]Computational Life Sciences, Life & Medical Sciences (LIMES) Institute, University of Bonn, Germany; [2]Bonn Center for Mathematical Life Sciences, University of Bonn, Germany; [3]Developmental Biology of the Immune System, Life & Medical Sciences (LIMES) Institute, University of Bonn, Germany; [4]Biochemistry & Cell Biology of Lipids, Life & Medical Sciences (LIMES) Institute, University of Bonn, Germany; [5]Clinical Institute of Pathology, Department for Experimental and Laboratory Animal Pathology, Medical University of Vienna, Vienna, Austria; [6]Comprehensive Cancer Center, Medical University Vienna, Vienna, Austria; [7]Unit of Laboratory Animal Pathology, University of Veterinary Medicine Vienna, Vienna, Austria; [8]Department of Molecular Biology, Umeå University, Umeå, Sweden; [9]Christian Doppler Laboratory for Applied Metabolomics, Medical University Vienna, Vienna, Austria; [10]Center for Biomarker Research in Medicine (CBmed), Graz, Styria, Austria; [11]Systems Medicine, Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE) e.V., Bonn, Germany; [12]Genomics & Immunoregulation, Life & Medical Sciences (LIMES) Institute, University of Bonn, Bonn, Germany; [13]PRECISE Platform for Single Cell Genomics and Epigenomics, DZNE and University of Bonn and West German Genome Center, Bonn, Germany; [14]Department of Internal Medicine and Paediatrics, Hepatology Research Unit, Ghent University, Ghent, Belgium; [15]Laboratory of Myeloid Cell Biology in Tissue Damage and Inflammation, VIB-UGent Center for Inflammation Research, Ghent, Belgium; [16]Department of Biomedical Molecular Biology, Faculty of Science, Ghent University, Ghent, Belgium; [17]Laboratory of Myeloid Cell Biology in Tissue Homeostasis and Regeneration, VIB-UGent Center for Inflammation Research, Ghent, Belgium; [18]Shanghai Institute of Immunology, Department of Immunology and Microbiology, Shanghai Jiao Tong University School of Medicine, Shanghai, China; [19]INSERM U1015, Gustave Roussy Cancer Campus, Villejuif, France; [20]Singapore Immunology Network, Agency for Science, Technology and Research, Singapore, Republic of Singapore; [21]Translational Immunology Institute, SingHealth Duke-NUS Academic Medical Centre, Singapore, Republic of Singapore; [22]Immunogenomics & Neurodegeneration, Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE) e.V., Bonn, Germany; [23]Institute of Innate Immunity, Department of Systems Immunology and Proteomics, Medical Faculty, University of Bonn, Bonn, Germany; [24]Institute of Innate Immunity, Biophysical Imaging, Medical Faculty, University of Bonn, Bonn, Germany

*equal contribution

Kupffer cells (KCs), the liver-resident macrophages, differentiate during embryogenesis and play central role in maintaining hepatic and systemic homeostasis. While it is known that KCs' transcriptional program are shaped upon colonization in the liver during embyogenesis and maturation, the impact of developmental disturbances remains poorly understood. In this study, we used a mouse model of maternal obesity to investigate whether perturbations in KC development contribute to long-term metabolic disease in offspring. A comprehensive multi-omics approach was utilized, encompassing cell type-specific transcriptomics (bulk RNA-seq of sorted KCs), liver lipidomics, serum metabolomics, and single-nucleus multiome sequencing (snRNA-seq and snATAC-seq of liver tissue). This integrative strategy enabled the assessment of transcriptional, metabolic, and epigenetic alterations of KCs and their consequencial crosstalk change with hepatocytes. Our analyses revealed that offspring exposed to maternal obesity develop fatty liver disease, characterized by increased hepatic lipid accumulation and local inflammation, independent of postnatal diet. Transcriptional profiling of KCs from these offspring demonstrated a persistent shift from oxidative phosphorylation to glycolysis, indicating metabolic reprogramming. Gene co-expression network analysis identified upregulation of Hif1α target genes, including those involved in glycolysis and inflammatory responses. Single-nucleus multiome data further confirmed increased chromatin accessibility at Hif1α-responsive elements in KCs, corroborating the transcriptional findings. Functional assays demonstrated that KCs having experienced maternal obesity induced lipid droplet

accumulation in primary hepatocytes through paracrine signaling in disease pathogenesis. Importantly, genetic ablation of Hif1a in myeloid cells during gestation restored KC transcriptional profiles and prevented the development of fatty liver disease in offspring, underscoring the critical role of Hif1α in mediating these effects. Collectively, our multi-omics analytic strategy in combination with functional assays, and various mouse models delineate a mechanistic link between maternal obesity and offspring fatty liver disease, mediated by Hif1α-dependent developmental programming of KCs. These findings position fetal-derived macrophages as intergenerational messengers within the concept – developmental origins of health and disease.

For full details, see our primary publication: Huang H, Balzer NR, Seep L, et al. Kupffer cell programming by maternal obesity triggers fatty liver disease. *Nature*. 2025;644(8077):790-798. doi:10.1038/s41586-025-09190-w

Visual Insights into Complex Dynamical Systems via Flux Sensitivity Analysis

Paul Sellentin[1], Fabian Konrath[2], Rafael Arutjunjan[1], Jens Timmer[1], Jana Wolf[2]

[1]Physikalisches Institut, Albert-Ludwigs Universität Freiburg, Freiburg, Germany; [2]Max Delbrück Center, Berlin, Germany

In the life sciences, a wide range of biological processes can be mechanistically described using models based on differential equations. Over the past decade, advances in experimental techniques have led to a significant increase in the amount of available data and thus resulted in the development of larger and more ambitious mathematical models. As the size and complexity of typical models rise, the combinatorial interplay of their constituent mechanisms often becomes too intricate to understand on an intuitive level, even though each mechanism can be understood in isolation. Therefore, the need for systematic approaches to analyse such complex systems efficiently and extract actionable insights has also grown. To address this challenge, we present an analytical method that provides a quantitative assessment of the sensitivity of individual mechanisms or components in a system with respect to outside perturbation. Furthermore, the relative sensitivity and influence of different targets in a system usually change over time, which means that there is rarely a singular driver of the overall behaviour, but rather different drivers at different time points. Through visualisation of our proposed time-resolved relative sensitivities, these complex interactions between mechanisms are condensed into a manageable form and can thus be understood much more intuitively. By identifying which targets are most sensitive to external perturbations at a given time, it becomes evident how the system can best be steered towards a desired goal state. In particular, this approach to targeted control is also useful in the development of personalised medicine, where treatment strategies are optimised for individual patients, not only in terms of dose, but also in terms of the time at which it is most effective to administer pharmaceutical agents. The simplicity and explanatory power of the proposed approach are shown with several case studies using established biological signalling models, demonstrating its ability to uncover and quantify the primary drivers of overall system behaviour within complex mechanistic regulatory networks over time.

The Inhibitome: A Genome-Wide Map of Inhibitory Gene Relationships

Angela Shaw[1], Jasper Spitzer[2]

[1]Institute of Human Genetics, University of Bonn, School of Medicine and University Hospital Bonn, Germany; [2]Institute of Innate Immunity, University Hospital Bonn, Germany

Genetic screens have traditionally focused on positive associations to map functional gene relationships. Here, we introduce the Inhibitome, a comprehensive resource of inhibitory gene relationships derived from negative genetic associations identified in a genome-wide CRISPR screen across ~300 diverse genetic backgrounds. Using a "guilt-by-opposition" framework, we systematically identify gene pairs with anti-correlated patterns that predict functionally antagonistic relationships. The Inhibitome connects genes within regulatory mechanisms, revealing significant enrichment for tumor suppressors and clinically actionable targets. Evolutionary analysis reveals that Inhibitome pairs are frequently younger, suggesting that inhibitory relationships may have emerged more recently to support homeostatic control in more complex organisms. Gene age further enables directional inference within pairs, distinguishing inhibitors from their targets. This yields testable clinical predictions: high expression of younger inhibitory genes should associate with improved patient survival, while their older inhibited partners should show opposite or neutral effects. These hypotheses will be tested through stratified survival analysis using TCGA datasets. Together, the Inhibitome demonstrates that large-scale genetic interaction screens can uncover biological relationships invisible to conventional approaches, and provides a resource for potential cancer drug targets based on evolutionarily-informed inhibitory relationships.

Embedding-Based Annotation Method in Adipose Tissue Spatial Metabolomics

Shenwei Shi[1], Joshua D. Rabinowitz[2,3,4], Tongtong Wang[1]

[1]Institute of Pharmacology and Toxicology, University of Bonn, Germany; [2]Department of Chemistry, Princeton University, Princeton, NJ, USA; [3]Lewis-Sigler Institute of Integrative Genomics, Princeton University, Princeton, NJ, USA; [4]Ludwig Institute for Cancer Research, Princeton University, Princeton, NJ, USA

Metabolomics and lipidomics provide high-resolution molecular maps of tissues, but accurate annotation remains challenging due to complex mass spectra and limited reference data. Traditional mass spectrometry (MS) annotation methods, relying on low-dimensional features (m/z, intensity) and similarity scores, are often insufficient for the high-dimensional nature of spatial datasets. Recent embedding-based approaches transform spectra into high-dimensional vectors, effectively grouping structurally similar molecules; however, this powerful technique has not been leveraged in spatial metabolomics and lipidomics. To achieve accurate and efficient spatially-resolved annotation, we introduce a novel framework. We leverage a curated in-silico lipid database to generate these spectral embeddings, enabling rapid candidate retrieval and precise scoring. Furthermore, the integration of a Transformer model provides advanced scientific reasoning, which significantly enhances annotation confidence and enables high-resolution spatial lipid mapping. This framework demonstrates a powerful combination of spectral embeddings, domain-specific knowledge bases, and advanced machine learning reasoning to substantially improve bioinformatics analyses in spatial metabolomics.

Biologically meaningful regulatory logic enhances the convergence rate in Boolean networks and bushiness of their state transition graph

Priyotosh Sil[1,2]*, Ajay Subbaroyan[1,2]*, Saumitra Kulkarni[1], Olivier C. Martin[3,4#], Areejit Samal[1,2#]

[1]The Institute of Mathematical Sciences (IMSc), Chennai, India; [2]Homi Bhabha National Institute (HBNI), Mumbai, India; [3]Université Paris-Saclay, CNRS, INRAE, Univ Evry, Institute of Plant Sciences Paris-Saclay (IPS2), Orsay, France; [4]Université de Paris, CNRS, INRAE, Institute of Plant Sciences Paris-Saclay (IPS2), Orsay, France

*shared first authorship; [#]shared last authorship

Boolean models of gene regulatory networks (GRNs) have gained widespread traction as they can easily recapitulate cellular phenotypes via their attractor states. Their overall dynamics are embodied in a state transition graph (STG). Indeed, two Boolean networks (BNs) with the same network structure and attractors can have drastically different STGs depending on the type of Boolean functions (BFs) employed. Our objective here is to systematically delineate the effects of different classes of BFs on the structural features of the STG of reconstructed Boolean GRNs while keeping network structure and biological attractors fixed, and explore the characteristics of BFs that drive those features. Using 10 reconstructed Boolean GRNs, we generate ensembles that differ in BFs and compute from their STGs the dynamics' rate of contraction or 'bushiness' and rate of 'convergence', quantified with measures inspired from cellular automata (CA) that are based on the garden-of-Eden (GoE) states. We find that biologically meaningful BFs lead to higher STG 'bushiness' and 'convergence' than random ones. Obtaining such 'global' measures gets computationally expensive with larger network sizes, stressing the need for feasible proxies. So we adapt Wuensche's Z-parameter in CA to BFs in BNs and provide four natural variants, which, along with the average sensitivity of BFs computed at the network level, comprise our descriptors of local dynamics and we find some of them to be good proxies for bushiness. Finally, we provide an excellent proxy for the 'convergence' based on computing transient lengths originating at random states rather than GoE states.

Curvature-Weighted Transmission Improves Network Epidemic Prediction and Control

Oladimeji Samuel Sowole[1,2], Nicola Luigi Bragazzi[1], Geminpeter A. Lyakurwa[2]

[1]African Institute for Mathematical Sciences, Research and Innovation Centre, Kigali, Rwanda; [2]The Nelson Mandela African Institution of Science and Technology, Arusha, Tanzania

We introduce a curvature-informed transmission kernel for network-based SIR model in which per-edge transmission rates are modulated by undirected Forman-Ricci curvature (FRC), a discrete descriptor of local redundancy and bridge-likeness. On Erdős-Rényi, Watts-Strogatz, Barabási-Albert, and Power-Law Cluster graphs, we calibrate a single baseline parameter β_0 on early epidemic trajectories and evaluate predictive accuracy on a holdout window. Against advanced baselines that weight transmission by edge-betweenness, eigenvector, or degree centrality, the FRC model yields consistent improvements in peak-time accuracy, holdout RMSE, and final-size proximity, especially on heterogeneous (hub-dominated) topologies. A compact global sensitivity analysis varying β_0 and each family's clustering parameter summarises robustness via (i) heatmaps of error deltas (baseline minus FRC), (ii) partial rank correlation coefficients with respect to β_0 and clustering, and (iii) aggregate win-rates across families; FRC remains favourable across regimes. Intervention ablations (expected cases averted vs. vaccination budget) further demonstrate operational value: prioritising high-curvature nodes and protecting extreme negative-curvature bridges outperforms edge-betweenness targeting across realistic budgets by combining intra-cluster suppression with spillover control. In general, curvature provides a principled geometric signal that enhances mechanistic forecast skill and yields concrete, topology-aware guidance for targeted vaccination and bridge protection. The framework is simple to compute, compatible with standard calibration workflows, and readily extensible to directed networks and learning-based predictors.

The AAtlas - Atlas of the Aorta in Health and Disease

Jasper Spitzer[1,2], Rául Jamin[3], Susanne V. Schmidt[1], Maximilian Billmann[2], Sebastian Zimmer[3]

[1]IKCKP, University Hospital Bonn, Germany; [2]Institute for Human Genetics, University Hospital Bonn, Germany; [3]Medizinische Klinik und Poliklinik II - Kardiologie, University Hospital Bonn, Germany

As the largest blood vessel in the body, the aorta is exposed to strong physical forces and is associated with several severe pathologies such as abdominal aortic aneurysm (AAA) or aortic valve stenosis (AS). These pathologies occur at specific locations, indicating a difference in local environment, not just physical but also reflected in the gene expression profiles of resident cells adapting to these forces. To elucidate the underlying heterogeneity, we performed single cell sequencing of four distinct sections along the mouse aorta, namely the ascending aorta, the aortic arch, the descending thoracic and abdominal aorta. Samples were collected in healthy mice as well as mice with aortic stenosis and abdominal aortic aneurysm after 28 days, profiling more than 380.000 cells from eight animals each for control, AAA and AS. We demonstrate location specific expression profiles in the major resident cell population, both derived from pattern specification through factors like HOX genes, and, more flexible, in response to injury. Having access to such data allows for in-depth profiling of pathway activities and transcriptional programs active along the aorta and if and how these patterns can persist in cases of structural failure. Additionally, resident and invading immune cell populations are profiled, revealing immune-extracellular matrix interactions at the center of the aortic pathologies. Together, our analyses reveal the structural heterogeneity along the human body's largest blood vessel and the cell-cell communications underlying the localization of AAA or the adaptations in the aorta following aortic stenosis.

Morpheus 3.0: Spatial reaction dynamics in deforming cell shapes

Jörn Starruß, Diego Jahn, Lutz Brusch

Center for Interdisciplinary Data Sciences, TU Dresden, Germany

When cells evolve into functional tissues they necessarily reshape and migrate into specific order. During this process cytosolic solutes are actively and passively redistributed and the cytoskeleton is actively remodeled.

The multicellular modelling framework Morpheus[1] is using the Cellular Potts model paradigm (CPM) to represent motile cell shapes and govern their temporal evolution. We present an extension for this framework that couples the stochastic temporal evolution of cell shapes to the spatial reaction dynamics of intra-cellular scalar fields. Specific strategies have been developed to model on one hand the redistribution of solutes and on the other the active remodeling of the cytoskeleton during migration.

With this extension, Morpheus can address for example the morphodynamic feedback loop of spatio-temporal patterns of signaling molecules like Rho and Rac GTPases and their effects on cell polarity and cell shape dynamics.

1. https://morpheus.gitlab.io

Predicting Vedolizumab Response in IBD Patients Using a Multimodal Machine Learning Approach

Lisa Maria Steinheuer[1], Veronika Horn[2], Camila Cancino[2], Benedikt Obermayer[3], Jonas Wehrenberg[4], Andreas Hutloff[4], Ahmed Hegazy[2], Kevin Thurley[1]

[1]Institute for Experimental Oncology, Biomathematics Division, University Hospital Bonn, Bonn, Germany; [2]Charité–Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Department of Gastroenterology, Infectious Diseases and Rheumatology, Berlin, Germany; [3]Berlin Institute of Health at Charité–Universitätsmedizin Berlin, Core Unit Bioinformatics, Berlin,Germany; [4]Institute of Immunology, University Hospital Schleswig-Holstein, Kiel, Germany

Inflammatory Bowel Disease (IBD) is a heterogeneous disorder, and up to 30% of patients fail to respond to Vedolizumab, a monoclonal antibody targeting T-cell migration. Identifying predictive markers prior to treatment could improve patient stratification and therapeutic outcomes. We analyzed a multimodal dataset comprising 126 features, including CyTOF, flow cytometry (FACS), OLINK proteomics, and clinical parameters.[1] Logistic regression classifiers were trained on individual and combined datasets, and model performance was validated using a workflow optimized for small patient cohorts. FACS and OLINK data provided the highest predictive power, both individually and in combination. Three of the four top-performing models were successfully validated, with Ki67 emerging as a consistent and strong predictor of Vedolizumab response, confirmed in an external cohort. Feature importance analysis revealed a strong contribution of FACS markers, while several chemokine receptors were among the most predictive features, suggesting that dysregulated T-cell communication contributes to treatment resistance. By integrating multimodal immune profiling with machine learning, we identified a clinically applicable biomarker panel capable of predicting Vedolizumab response before treatment initiation. This finding underscores the need for further investigation through, for example, mathematical modeling or functional studies to mechanistically dissect T-cell–mediated resistance.[2] Given the role of T-cell dysregulation in autoimmune diseases, we have already applied cell-cell communication analysis to identify disease-specific immune interactions, offering deeper insights into the mechanisms underlying immune dysfunctions.[3] Incorporating spatial transcriptomics will further enhance the ability to map cytokine niches, discover spatial cytokine networks, and immune interactions in situ. Beyond IBD, these approaches can be applied to study early T–B cell dynamics in lymph nodes using an adoptive transfer model, offering a framework to understand immune regulation across autoimmune contexts.[4]

References:

1. Horn V, Cancino CA, Steinheuer LM, et al. Multimodal Profiling of Peripheral Blood Identifies Proliferating Circulating Effector CD4+ T Cells as Predictors for Response to Integrin α4β7-Blocking Therapy in Inflammatory Bowel Disease. *Gastroenterology*. 2025;168(2):327-343. doi:10.1053/j.gastro.2024.09.021
2. Steinheuer LM, Klümper N, Bald T, Thurley K. Untangling cell–cell communication networks and on-treatment response in immunotherapy. *Curr Opin Syst Biol*. 2025;40: 100534. doi:10.1016/j.coisb.2024.100534
3. Kwon G, Wiedemann A, Steinheuer LM, et al. Transcriptional profiling upon T cell stimulation reveals down-regulation of inflammatory pathways in T and B cells in SLE versus Sjögren's syndrome. *npj Syst Biol Appl*. 2023;9(1):62. doi:10.1038/s41540-023-00319-z
4. Ritzau-Jost J, Hutloff A. T Cell/B Cell Interactions in the Establishment of Protective Immunity. *Vaccines*. 2021;9(10):1074. doi:10.3390/vaccines9101074

A General Deterministic Model of Ordinary Differential Equations for a Broad Variety of Different Diseases

Christoph Sticha-Kaiser[1,2], Christina Kuttler[3], Michael Hoelscher[1,2,4,5], Andreas Wieser[1,2,4,6], Noemi Castelletti[1,2,7]

[1]Institute of Infectious Diseases and Tropical Medicine, LMU University Hospital, Munich, Germany; [2]Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology, Infection and Pandemic Research, Munich, Germany; [3]Department of Mathematics, Technical University of Munich, Garching, Germany; [4]German Centre for Infection Research, Partner Site Munich, Germany; [5]Unit Global Health, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany; [6]Max von Pettenkofer Institute for Hygiene and Medical Microbiology, LMU Munich, Munich, Germany; [7]Institute of Radiation Medicine, Helmholtz Center Munich, Neuherberg, Germany

The COVID-19 pandemic underscored the pivotal role of mathematical models in understanding pandemic dynamics and making accurate predictions under diverse interventions. Various mathematical models, particularly deterministic ones, have proven valuable for analyzing the impact of political, social, and medical measures during ongoing pandemics. In this study, we aim to formulate and characterize a comprehensive model applicable to different infectious diseases. Reviewing numerous disease-specific models reveals a common foundation in the Kermack-McKendrick model (SIR model). While there are more general versions incorporating population dynamics, vector populations, and vaccination, none encompass all attributes simultaneously. To address this gap, we propose a comprehensive general model capable of accommodating different transmission modes, pandemic control measures, and diverse pathogens. Unlike disease-specific models, such a pre-established model, with foundational mathematical properties analyzed, eliminates the need to reevaluate these characteristics for each new disease-specific model. Our approach aims to streamline the modeling process, enhancing flexibility and accuracy in simulating a broad range of infectious disease scenarios. We present our comprehensive general model, supported by mathematical analysis and numerical simulations, offering a versatile tool for understanding the dynamics of emerging infectious diseases and guiding intervention strategies. The model incorporates key features such as various transmission routes (e.g., airborne, vector-borne, smear, and direct contact) and multiple intervention strategies, including quarantine, vaccination, and social distancing measures. Moreover, testing and detection dynamics can explicitly be analyzed, including different testing strategies or potential underreporting. To demonstrate the applicability of our model, we apply it to several well-known pathogens — Ebola, Varicella, Plague, and COVID-19 — using real outbreak data. For each disease, the model accurately reflects the pathogen's specific transmission dynamics and intervention strategies. For instance, while COVID-19 is primarily airborne, Ebola spreads through direct contact with bodily fluids, and Plague involves both airborne and vector-borne transmission. Our model adapts to these differing modes of transmission while maintaining the underlying structure. Simulations, calibrated using real-world outbreak data, show that the model effectively predicts disease spread and outcomes under various intervention scenarios. This highlights the model's potential to support decision makers in future outbreaks.

Understanding cross-regulation of type I IFN and TNF in innate immune cells using data-driven mathematical modelling

Madheshvaran Suresh[1], Lisa M. Steinheuer[1], Benjamin Krämer[2], Jacob Nattermann[2], Kevin Thurley[1]

[1]Institute of Experimental Oncology, University Hospital Bonn, Germany; [2]Laboratory for Innate Cellular Immunology, University Hospital Bonn, Germany

The cross-regulation of type I IFN and TNF has an intricate interplay on innate and adaptive immune cells, contributing to immune homeostasis; dysregulation in this cross-talk promotes inflammation, autoimmunity, and allergic reactions.[1] In particular, type I IFN and TNF have been identified as essential elements influencing the pathophysiology of COVID-19.[2] Understanding the TNF/IFN cross-regulation in the context of viral infections, such as COVID-19, has been challenging due to practical concerns associated with the system's high biological complexity. Systematic data analysis of single-cell data (such as longitudinal scRNA-seq and highly time-resolved flow cytometry data), combined with mathematical modelling, is used to tackle this challenge, providing insights into understanding cell-cell communication dynamics under different in silico perturbatory conditions.[3,4] In this project, we aim to develop a data-driven mathematical model that combines quantitative data analysis and mechanistic modelling approaches to gain a quantitative understanding of the early immune responses to viral infections, and to identify factors contributing to differential disease outcomes. We established a workflow to identify kinetic gene expression patterns from longitudinal single-cell transcriptomic[5] and flow cytometric data in NK cells. Additionally, our preliminary knowledge-driven model captures the TNF/IFN interplay in innate cells, including NK cells, macrophages and pDCs, at the onset of viral infection. The insights garnered from this project in understanding how to modulate the TNF/IFN interplay effectively can help identify the factors leading to differential disease progression trajectories. The formulated data-driven model will be used in the generation of kinetic in silico perturbation datasets, shedding light on the role of TNF/IFN interplay in driving hyperinflammation, a critical aspect not only in COVID-19 but also in other viral diseases and sepsis.

References:

1. Cantaert T, Baeten D, Tak PP, van Baarsen LG. Type I IFN and TNFα cross-regulation in immune-mediated inflammatory disease: basic concepts and clinical relevance. *Arthritis Res Ther*. 2010;12(5):219. doi:10.1186/ar3150
2. Krämer B, Knoll R, Bonaguro L, et al. Early IFN-α signatures and persistent dysfunction are distinguishing features of NK cells in severe COVID-19. *Immunity*. 2021;54(11):2650-2669.e14. doi:10.1016/j.immuni.2021.09.002
3. Steinheuer LM, Klümper N, Bald T, Thurley K. Untangling cell–cell communication networks and on-treatment response in immunotherapy. *Curr Opin Syst Biol*. 2025;40: 100534. doi:10.1016/j.coisb.2024.100534
4. Burt P, Thurley K. Distribution modeling quantifies collective T_H cell decision circuits in chronic inflammation. *Sci Adv*. 2023;9(37):eadg7668. doi:10.1126/sciadv.adg7668
5. Burt P, Peine M, Peine C, et al. Dissecting the dynamic transcriptional landscape of early T helper cell differentiation into Th1, Th2, and Th1/2 hybrid cells. *Front Immunol*. 2022;13:928018. doi:10.3389/fimmu.2022.928018

Evaluating the impact and effectiveness of HIV testing strategies among men who have sex with men in the Netherlands

Alexandra Teslya[1], Jacob Roberts[1], Janneke Heijne[2,3], Maarten Schim van der Loeff[2,3], Ard van Sighem[4], Axel Schmidt[5,6], Kai Jonas[7], Mirjam Kretzschmar[1,8], Ganna Rozhnova[1,8,9,10]

[1]University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands; [2]Public Health Service of Amsterdam, Amsterdam, The Netherlands; [3]Amsterdam Institute for Immunology and Infectious Diseases, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands; [4]Stichting hiv monitoring, Amsterdam, The Netherlands; [5]Sigma Research, Department of Public Health, Environments and Society, London School of Hygiene and Tropical Medicine, London, United Kingdom; [6]Medicine and Health Policy Unit, German AIDS Federation, Berlin, Germany; [7]Faculty of Psychology and Neuroscience, Maastricht University, The Netherlands; [8]Center for Complex Systems Studies (CCSS), Utrecht University, Utrecht, The Netherlands; [9]BioISI – Biosystems & Integrative Sciences Institute, Faculdade de Ciências, Universidade de Lisboa, Lisboa, Portugal; [10]Faculdade de Ciências, Universidade de Lisboa, Lisbon, Portugal

Background: Although the number of new HIV diagnoses among men who have sex with men (MSM) in the Netherlands has declined considerably, the recent plateau in this metric suggests ongoing transmission. In 2023, 30% of new diagnoses among MSM were in a late HIV stage, indicating opportunities for earlier detection. In low-incidence settings, testing strategies must be refined to identify cases that broader screening practices do not capture. Meanwhile, the role of infections acquired abroad in sustaining transmission grows in importance. We aim to assess the impact of targeted testing strategies among MSM in the Netherlands which address these considerations. Methods: We extended a published agent-based model of HIV transmission among MSM in the Netherlands, accounting for infections acquired both domestically and abroad. The model was parameterised using Dutch sexual behaviour data and HIV surveillance data from 2017-2023. In 2023-2024 the model proceeded without interventions other than HIV care services and PrEP programme currently active in the Netherlands. In 2025-2040 we simulated targeted testing interventions, which included offering an HIV test to immigrants upon entry into the country and increasing testing rates in subgroups of MSM residing in the Netherlands. Impact of the interventions was measured as cumulative number of new HIV infections averted compared to baseline (only HIV care services and PrEP programme). Results: In the baseline scenario, the model projects a median of 1,178 new HIV infections over 15 years (95% quantile interval [95%QI]: 840–1,596). Intervention when 50% of incoming immigrants get tested at entry and the general MSM population tests every 7 month results in the greatest reduction in new infections among all evaluated interventions, 536 cases (95% QI: 312-792). A similar impact was observed when only 25% of incoming immigrants get tested at entry (534, 95%QI: 308-884). Intervention with MSM with >5 partners in the previous 6 months test with frequency of every 7 months and either 25% or 50% of incoming immigrants getting tested averts 380 (95% QI 148-672) and 390 (95% QI 180-708) HIV infections. Implications: Combining a testing offer to incoming immigrants at entry and a testing frequency of every 7 months in the general MSM population or, more efficiently, in MSM in a “high number of partners” subgroup can avert HIV infections substantially. Additionally, offering testing at entry would provide health benefits due to earlier linkage to care, which otherwise they might access less readily than long-term residents.

Comparison of discrete modelling methods for biological neural networks

Jan Tietgen

CAU Kiel, Germany

Modelling biological systems using the mathematical framework of discrete-valued multivariate functions has been done rather successfully and extensively in recent times. One area of application is the field of biological neural networks, where modelling of networks can be achieved using the so-called SER formalism. Here, S, E and R stand for susceptible, excited and refractory, respectively, and can be viewed as the possible levels of activity of a given neurone in a neural network. Then looking at all n neurones and their respective levels of activity $\mathrm{S}, \mathrm{E}, \mathrm{R}$ and assuming discrete time, we can view such a network as a specific discrete-valued multivariate function with values in $\{\mathrm{S}, \mathrm{E}, \mathrm{R}\}^{\mathrm{n}}$, where each state of the network is mapped to the subsequent state. Another, more general way of modelling biological networks utilises Boolean functions and their dynamics. The general idea is to assume a set of n many components of a network and then model their activity at a given point in time as either 1, meaning active, or 0, meaning inactive. Then, similar to the SER modelling approach, one can view a biological network as a discrete-valued multivariate function with values in $\{0,1\}^{\mathrm{n}}$, where each state of the network is mapped to the subsequent state. Depending on the preferred dynamics, such a subsequent state must always exist but not necessarily be uniquely determined. In the past, both of these ways of modelling have been applied to related types of biological systems and used to answer alike questions but were mostly studied independently of each other. Specifically for Boolean functions, a large set of tools and theory exists which we believe to be of interest for the analysis of neural networks as well. We make a connection of these two modelling approaches the following way: A neurone can be viewed as active if it is excited and as inactive otherwise. With this correspondence we can associate to a given SER model of a neural network a Boolean function. This allows us to apply the associated theory and transfer results from the world of Boolean functions to SER models. We show that since this association of a Boolean function does not differentiate between the state of a neurone being either susceptible or refractory, our approximation of an SER network through a Boolean function cannot be 1-to-1. We address this by using an asynchronous, nondeterministic dynamics for the Boolean function, which leads us to an overapproximation containing as a substructure essentially the whole SER network we started with. In the context of this overapproximation, we also present some new results connecting the dynamical behaviour of SER models to the structure of the network that they model. Similar results already exist for the dynamics of Boolean functions and the structure of their associated interaction graphs.

Image-Based Quantification of Autophagosome Biogenesis

Frédéric Sonak[1,2], Franziska Kriegenburg[2], Claudine Kraft[2], Viviane Timmermann[1,3]

[1]Institute of Physics, University of Freiburg, Germany; [2]Institute of Biochemistry and Molecular Biology, University of Freiburg, Germany; [3]Institute of Molecular Medicine and Cell Research, University of Freiburg, Germany

Autophagy is a vital cellular recycling mechanism that helps to maintain homeostasis, supports adaptation to stress, and is associated with pathologies such as neurodegeneration, cancer, and inflammation. The hallmark of this process is the formation of double-membrane vesicles, known as autophagosomes, which enclose cytoplasmic material for degradation in the lytic compartment. Although many molecular components of the autophagy machinery have been identified, the spatiotemporal coordination of autophagosome formation and the functional organisation of autophagy-related proteins remain only partly resolved. To address this challenge, we integrate computational image analysis with artificial intelligence-based feature detection to obtain quantitative insights into autophagy dynamics. Using high-resolution fluorescence microscopy of yeast cells, we developed a machine learning-assisted pipeline for automated segmentation and extraction of features such as vesicle geometry and protein localisation. Novel morphometric metrics allow consistent quantification of autophagic structures and their dynamic changes. Designed for transparency and usability, these tools provide a robust framework for objective, data-driven analysis and promote the broader adoption of quantitative approaches in cell biology.

STAT1–p53 Dynamics Program Cell Fate through p21 and PUMA

Francis Didier Tshianyi Mwana Kalala[1,2], Didier Gonze[1], Rebecca Walo Omana[3]

[1]Université libre de Bruxelles, Belgium; [2]University of Lubumbashi, Congo (Democratic Republic); [3]University of Kinshasa, Congo (Democratic Republic)

Cell-fate decisions under stress are governed by the dynamic interplay between the tumour suppressor p53, its negative regulator Mdm2, and downstream effectors such as p21 and PUMA. While p53 stabilisation through attenuation of the p53–Mdm2 feedback is well established, the quantitative impact of Signal Transducer and Activator of Transcription 1 (STAT1)—which both represses *Mdm2* transcription and co-activates p53 target genes—has remained largely unexplored. We present a mechanistic mathematical model that explicitly couples a calibrated stress variable (S) and STAT1 activity (Σ) to the canonical p53–Mdm2 loop and its *p21* and *PUMA* branches. Kinetic rates are formulated as explicit functions of stress, allowing the system to self-adjust across stress levels and reproduce oscillatory, damped, or plateau dynamics. Bifurcation analysis reveals a two-dimensional Hopf region in the S, Σ plane, showing that increasing Σ shifts and compresses the oscillatory domain, ultimately suppressing p53 pulses at high STAT1 activity. STAT1 thus acts as both an amplifier and an oscillation quencher within the p53 network. A two-stage decision rule, combining early transient detection with a stationary readout, maps p53-driven dynamics onto cell-fate outcomes. Sustained moderate oscillations correlate with reversible arrest of the cell cycle, damped intermediate responses with senescence, and strongly damped high plateaux with apoptosis. Simulations of heterogeneous cell populations reproduce experimental fate distributions for archetypal lines (MCF-7, HCT116, U2OS), revealing lineage-specific sensitivity to *p21* versus *PUMA*. This integrative framework establishes a quantitative link between stress intensity, STAT1 signalling, and downstream fate control. It provides a predictive, dynamical basis for interpreting how cytokine signalling and DNA damage jointly govern p53 responses, offering experimentally testable hypotheses on how stress–STAT1 cooperation modulates survival, arrest, or apoptosis across cell types.

Uncertainty-Aware Diversity Quantification via the Chinese Restaurant Process

Marc Vaisband[1,2], Christian Scherhäufl[3], Stephan Drothler[3], Nadja Zaborsky[3], Jan Hasenauer[1,2]

[1]LIMES Institute, University of Bonn, Germany; [2]Center for Mathematical Life Sciences, University of Bonn, Germany; [3]Department of Internal Medicine III with Haematology, Medical Oncology, Haemostaseology, Infectiology and Rheumatology, Salzburg University Hospital, Salzburg, Austria

Diversity is central to many biological systems, from gut microbiome balance to transcriptional heterogeneity and tumour clonality, but is often summarised by point estimates such as Shannon or Simpson indices that ignore sample size and associated uncertainty. We instead quantify diversity via the dispersion parameter ϑ of the Chinese Restaurant Process (CRP), a truncated Poisson–Dirichlet Process over integer-valued partitions, where ϑ directly controls the probability that an additional observation forms a previously unseen class. We derive and implement a closed-form likelihood for observing a partition given ϑ in an optimised Julia framework, enabling efficient uncertainty-aware estimation and permutation-based likelihood ratio tests for equality of diversities. The CRP estimator is stable under sub-sampling, ensuring that finite-sample effects are properly accounted for. Embedding this likelihood in a generalized linear mixed-effects model structure further allows us to assess the influence of arbitrary covariates and random effects on diversity. Using synthetic benchmarks and single-cell sequencing data, we show that this framework uncovers between-group diversity differences that standard indices fail to detect, providing a principled and flexible alternative for diversity analysis.

Enhanced neutrophil infiltration and distinct spatial patterning in non-draining lymph nodes under adoptive T cell therapy in murine melanoma

Gemma van der Voort[1,2]*, Maike Effern[3]*, Michelle Yong[3], Lukas Kiwitz[3], Roberta Turiello[3], Sonia Leonardelli[3], Susanna Ng[3], Dillon Corvino[3], Tobias Bald[3], Nicole Glodde[3], Kevin Thurley[3], Jan Hasenauer[1,2], Michael Hölzel[3]

[1]Life and Medical Sciences (LIMES) Institute, University of Bonn, Bonn, Germany; [2]Bonn Center for Mathematical Life Sciences, University of Bonn, Bonn, Germany; [3]Institute of Experimental Oncology, University Hospital Bonn, Bonn, Germany

*shared first authorship

Neutrophils infiltrate the tumor-draining lymph node (tdLN) during cancer progression, where they play an initially anti-, but later pro-tumorgenic role. They acquire immunosuppressive properties that can hamper the CD8+ T cell response during adoptive T cell therapy (ACT). How the neutrophil dynamics and interactions are shaped during ACT in not only the tdLN but also the non-draining lymph nodes is not yet well understood. Leveraging flow cytometry and CODEX data, we characterized the neutrophil and tumor-specific CD8+ T cell population throughout ACT and across both draining and non-draining lymph nodes. We found that the non-draining lymph node contains significantly more neutrophils than the tdLN, and that neutrophils form distinct spatial patterns in the draining and non-draining lymph nodes. Upon innate immune stimulation, neutrophil infiltration was most pronounced in the non-draining lymph node, where neutrophil abundance is positively correlated with abundance of short-lived CD8+ T cells. These results suggest that neutrophils in the draining and non-draining lymph nodes play different roles under ACT and highlight the importance of understanding the spatial and functional distribution of neutrophils in ACT and related immunotherapies.

Do metrics from ecology help to classify clonal immune dynamics from T cell receptor repertoire data?

Szilard Varga[1], Kerem Fikri Kinal[2], Yusuf Turhan[2], Jürgen Pahle[2], Frederik Graw[1,3,4]

[1]Department of Internal Medicine 5, Haematology and Oncology, Friedrich-Alxander-Universität Erlangen-Nürnberg and Universitätsklinikum Erlangen, Erlangen, Germany; [2]Biological Information Processing Group, BioQuant, Heidelberg University; Heidelberg, Germany; [3]Deutsches Zentrum Immuntherapie (DZI), FAU Erlangen-Nürnberg and Universitätsklinikum Erlangen, Erlangen, Germany; [4]Bavarian Cancer Research Centre (BZKF), Erlangen, Germany

T cell immunity, a central component of the adaptive immune system, relies on the exceptional diversity of T cell receptors (TCRs) to recognize infected or malignant cells. The TCR repertoire encodes the antigen recognition landscape and thereby governs the highly dynamic processes of recruitment and maintenance of antigen-specific T cells. Sequencing TCR repertoires, typically from peripheral blood, has become a standard approach to characterize immune responses to infection, vaccination and cancer. Such repertoire snapshots reveal the clonal structure of T cell populations and provide valuable insights into polyclonality, epitope escape, and immune memory formation. However, to which extent changes in clonal composition relate to clonal dynamics still remains elusive. Here, we explored how repertoire-level information can be leveraged to infer clonal dynamics and identify distinct patterns of T cell behavior in simulated immune responses. Following Venturi et al.,[1,2] we borrowed concepts from ecology, and adapted several diversity and similarity metrics, including the Simpson's diversity index, as well as the Morisita-Horn and Chao-Jaccard similarity indices to quantify heterogeneity and overlap across TCR samples. However, we further extended these metrics by estimating individual clonal contributions through delete-1 jackknife resampling, enabling the inference of clonal-level dynamics. Using a bottom-up approach, we studied the applicability of these metrics across a range of simulated clone size distributions. To model the temporal evolution of TCR repertoires, we developed a stochastic framework simulating a prime-boost vaccination scheme, which incorporates three distinct clonal dynamics distinguishing between (i) persistent clones that remain abundant throughout the simulation, (ii) contracting clones that diminish despite re-stimulation, and (iii) late-emerging clones that expand only upon later challenges. We simulated TCR evolution and repertoire sampling at multiple time points following repeated antigen exposures and estimated corresponding diversity and similarity indices. Preliminary analyses of these annotated synthetic datasets using various machine learning (ML) approaches suggest that distinct clonal behaviors can be inferred from TCR repertoire evolution data. Thus, longitudinal repertoire sequencing and the combination of ecological diversity measures could help to infer T cell clonal dynamics, which may enhance our understanding of vaccine-induced immunogenicity.

1. Venturi V, Kedzierska K, Turner SJ, Doherty PC, Davenport MP. Methods for comparing the diversity of samples of the T cell receptor repertoire. *J Immunol Methods*. 2007;321(1-2):182-195. doi:10.1016/j.jim.2007.01.019
2. Venturi V, Kedzierska K, Tanaka MM, Turner SJ, Doherty PC, Davenport MP. Method for assessing the similarity between subsets of the T cell receptor repertoire. *J Immunol Methods*. 2008;329(1-2):67-80. doi:10.1016/j.jim.2007.09.016

Modelling a potential spread of Foot-and-Mouth disease on the German animal trading networks

Kilian Volmer[1], Jörn Gethmann[2], Julia Bicker[3], René Schmieding[3], Hannes Bergmann[2], Christoph Staubach[2], Jana Schulz[2], Martin Kühn[1,3], Carola Sauter-Louis[2], Jan Hasenauer[1]

[1]University of Bonn, Germany; [2]Friedrich-Loeffler-Institut, Greifswald - Insel Riems, Germany; [3]DLR, Cologne, Germany

In January 2025, the first outbreak of the Foot-and-Mouth Disease (FMD) for more than 30 years has been detected in Germany. Several FMD simulation models already exist, but they have some disadvantages: There code is not freely accessible and long runtimes limit quick scenario evaluations needed for decision-making. For spatial spreading across herds, one of the main transmission pathways is trade with infected animals. The animal trade network in Germany is very well documented, consisting of about 1.5 million edges in pig trade and 1.8 million in cattle trade per year. Working with large-scale datasets requires efficient and scalable simulation software. One such software package is the open-source "Modular EpideMIcs Simulation Software" MEmilio that we adapted to simulate a potential outbreak of FMD on animal trading networks. In particular, we used the German cattle trading network based on individual animals, together with sheep and pig trading networks based on batches. We combined these datasets in a metapopulation based approach where spatial units were given by farms. Together with high performance computing infrastructure, this approach allowed the exploration of various intervention strategies in a short time to inform veterinary health authorities.

Wastewater-Informed Agent-Based Modeling of Hepatitis E Transmission Dynamics

Karina Wallrafen-Sam[1,2], Jasmin Javanmardi[4], Nina Schmid[1,2], Mathias Schemmerer[3], Jürgen J. Wenzel[3], Andreas Wieser[4,5,6,7], Jan Hasenauer[1,2]

[1]Life & Medical Sciences Institute (LIMES), University of Bonn, Germany; [2]Bonn Center for Mathematical Life Sciences, University of Bonn, Bonn, Germany; [3]National Consultant Laboratory for HAV and HEV, Institute of Clinical Microbiology and Hygiene, University Medical Center Regensburg, Regensburg, Germany; [4]Institute of Infectious Diseases and Tropical Medicine, LMU University Hospital Munich, Munich, Germany; [5]German Centre for Infection Research (DZIF), Partner Site Munich, Munich, Germany; [6]Max von Pettenkofer Institute, Faculty of Medicine, LMU Munich, Munich, Germany; [7]Immunology, Infection and Pandemic Research (IIP), Fraunhofer Institute for Translational Medicine and Pharmacology (ITMP), Munich, Germany

Wastewater-based epidemiology (WBE) is an emerging tool for infectious disease surveillance that mitigates underreporting bias by detecting viral material shed by infected individuals regardless of symptom or diagnosis status. WBE is particularly suited for monitoring the Hepatitis E virus (HEV), which is often clinically silent and has a very low estimated reporting rate in Germany, yet represents a growing public health concern due to recent reported case increases and the discovery of chronic hepatitis in immunosuppressed persons. In Germany, HEV is believed to be a foodborne infection that spreads primarily via the consumption of raw or undercooked pork. However, recent analyses of wastewater data from Munich revealed lower HEV concentrations during COVID-19 lockdowns, suggesting that transmission may be more sensitive to changes to human mobility and contact patterns than previously assumed. To investigate whether these reductions in wastewater HEV loads are consistent with transmission exclusively via contaminated food, we developed a network-based, city-scale mathematical model of HEV dynamics. The stochastic, individual-level model captures incident infections caused by consumption of undercooked pork, disease progression, differential case ascertainment by symptom status, viral shedding into the sewer system, and wastewater measurement noise. During lockdown periods, the baseline daily foodborne transmission probability was multiplied by a damping factor to capture the effects of behavioral changes such as reduced visits to restaurants. The model was calibrated using Approximate Bayesian Computation methods against longitudinal wastewater measurements collected during and after the COVID-19-related lockdowns of 2020 and 2021 from two sampling stations in Munich. Preliminary results provide evidence of reduced HEV transmission during lockdown periods, as the posterior distribution for the lockdown effect parameter has a 95% credible interval excluding one (i.e., no effect). Several mechanisms could explain this reduction, including decreased restaurant-related transmission or potential contributions from person-to-person spread. The model also reproduces the empirically observed lack of correlations between wastewater measurements and diagnoses, although the underlying processes are linked, due to the inherent high stochasticity of the low-case regime. Collectively, our findings demonstrate the value of combining wastewater epidemiology with individual-level mathematical modeling to deepen our understanding of pathogens that are difficult to monitor through traditional case-based methods.

Comparison of Simulation-based Inference Methods for Stochastic Compartmental Models

Nils Waßmuth[1]*, Vincent Wieland[2]*, Lorenzo Contento[3#], Martin Kühn[1#], Jan Hasenauer[2#]

[1]German Aerospace Center (DLR), Cologne, Germany; [2]University of Bonn, Germany; [3]Pumas-AI

*shared first authorship; [#]shared last authorship

Global pandemics, as the recent COVID-19 crisis, underscore the urgent need for advanced epidemic modeling techniques capable of capturing the inherent randomness in disease spread. This paper presents a comparison of two state-of-the-art Bayesian inference methods, Conditional Normalizing Flows (CNF) and pseudo-marginal particle Markov chain Monte Carlo, short Particle Filters (PF), applied to stochastic compartmental models. We investigate two commonly used compartmental models: a classical Susceptibel-Infected-Recovered (SIR) model and a two-variant Susceptible-Exposed-Infected-Recovered (SEIR) model, complemented by an observation model that maps theoretical trajectories to empirical data. Addressing the challenges of parameter inference in complex stochastic settings, our analysis highlights how these likelihood-free methods provide accurate and robust inference capabilities. The results of our simulation study further demonstrate the applicability of these approaches in capturing the stochastic dynamics of epidemics, providing prediction capabilities for the control of epidemic outbreaks. Results on an Ethiopian cohort study replicate these patterns and demonstrate operational robustness under real-world noise and irregular sampling. We release code and synthetic datasets to facilitate reuse and to spur pipelines that ultimately contribute to better informed decision making in public health.

PEtab, pyPESTO, and AMICI: A Reproducible and Efficient Pipeline for Simulation and Parameter Estimation of Dynamic Models

Daniel Weindl, The AMICI, PEtab, and pyPESTO contributors

University of Bonn, Germany

Reproducible and scalable parameter estimation for dynamic models remains a central challenge in systems biology, particularly as model complexity and data volume continue to grow. We present PEtab, pyPESTO, and AMICI, which together provide a streamlined workflow for specifying parameter estimation problems, simulating dynamic models, and performing efficient parameter estimation, especially for ordinary differential equation-based models. PEtab is a structured, tool-agnostic format for defining parameter estimation problems, including models, measurements, observables, and noise models. AMICI enables efficient simulation and sensitivity computation through optimized code generation and fast numerical solvers. pyPESTO integrates these components into an customizable framework for optimization, uncertainty quantification, and model selection, supporting multi-start strategies, global optimization, profile likelihoods, and sampling-based inference. Together, these tools establish an efficient computational pipeline that lowers barriers to model calibration, improves reproducibility and interoperability, and facilitates method comparisons. Their applicability has been demonstrated across diverse research projects, from small to large scale problems. We highlight current features, showcase ongoing developments, and look forward to engaging with current and future users.

References

- Schmiester L, Schälte Y, Bergmann FT, et al. PEtab-Interoperable specification of parameter estimation problems in systems biology. *PLoS Comput Biol*. 2021;17(1):e1008646. doi:10.1371/journal.pcbi.1008646
- Schälte Y, Fröhlich F, Jost PJ, et al. pyPESTO: a modular and scalable tool for parameter estimation for dynamic models. *Bioinformatics*. 2023;39(11):btad711. doi:10.1093/bioinformatics/btad711
- Fröhlich F, Weindl D, Schälte Y, et al. AMICI: high-performance sensitivity analysis for large ordinary differential equation models. *Bioinformatics*. 2021;37(20):3676-3677. doi:10.1093/bioinformatics/btab227

Models based on integro-differential equations for epidemic outbreaks

Anna Wendler[1], Lena Plötzke[1], Hannah Tritzschak[1], Martin J. Kühn[1,2]

[1]German Aerospace Center, Cologne, Germany; [2]University of Bonn, Germany

Ordinary differential equations (ODEs) are a popular tool to model the spread of infectious diseases, yet they implicitly assume an exponential distribution to describe the flow from one infection state to another. However, scientific experience yields more plausible distributions where the likelihood of disease progression or recovery changes accordingly with the duration spent in a particular state of the disease. Furthermore, transmission dynamics depend heavily on the infectiousness of individuals. The corresponding nonlinear variation with the time individuals have already spent in an infectious state requires more realistic models. The previously mentioned items are particularly crucial when modeling dynamics at change points such as the implementation of nonpharmaceutical interventions (NPIs). In order to capture these aspects and to enhance the accuracy of simulations, integro-differential equations (IDEs) can be used. To demonstrate the need for realistic assumptions regarding sojourn time distributions, we use an IDE-based model with eight infection states that allows for variable sojourn time distributions and generalizes the concept of ODE-based models. In particular, we include particular infection states for severe and critical cases to allow for surveillance of the clinical sector, avoiding bottlenecks and overloads in critical epidemic situations. We compare this model with sojourn time distributions according to data on COVID-19 to a corresponding ODE-based model. We observe differences regarding the size and timing of epidemic peaks. Furthermore, the IDE-based model displays a lag-time after the introduction of NPIs whereas the ODE-based model reacts immediately to a change in the contact rate. A drawback of IDE-based models is that standard numerical solvers for ODE systems cannot be applied and tailored schemes might be needed. We therefore present our research regarding different numerical schemes to solve systems of IDEs efficiently while preserving important mathematical and biological properties in the numerical solution.

Mathematical Inference of T-cell Trafficking Dynamics from Single-Cell Snapshots

Lennart Wicker[1], Szilard Varga[1], Frederik Graw[1,2,3]

[1]Department of Internal Medicine 5, Haematology and Oncology, Friedrich-Alexander-Universität Erlangen-Nürnberg and Universitätsklinikum Erlangen, Erlangen, Germany; [2]Deutsches Zentrum Immuntherapie (DZI), Erlangen, Germany; [3]Bavarian Cancer Research Centre (BZKF), Erlangen, Germany

T-cell trafficking is a complex and tightly regulated process influencing the functionality and effectiveness of adaptive immune responses. Cell trafficking interferes with cell proliferation and differentiation and is determined by specific surface markers and chemokine receptors expressed on the T-cell surface. As deviating trafficking patterns due to anomalous chemokine levels or receptor impairment can lead to pathological changes, such as immune-mediated inflammatory diseases, understanding the spatiotemporal dynamics of T-cell trafficking and its tight association to other processes is an important pre-requisite to develop novel therapeutic strategies against autoimmune disorders or malignant diseases. Although high-throughput single-cell profiling has become widely available and is frequently applied in immunology to characterize individual cell populations and their possible interactions, the direct inference of cellular trajectories from such snapshots is impossible due to the destruction of cells during the measurement process. A wide range of computational methods have been developed to probabilistically link cells either between samples or within a single snapshot to infer cellular differentiation trajectories. Yet, these methods are currently limited to infer couplings either across time or across space, but not both simultaneously. In addition, these methods often assume a linear differentiation process in contrast to the cyclic and partly transient nature of T-cell trafficking and differentiation dynamics. In order to overcome these limitations, and to develop and test novel mathematical methods to infer the intermingled dynamics of cell proliferation, differentiation and trafficking from standard single-cell snapshot data, we developed a stochastic, individual cell-based mathematical model in which proliferation, differentiation and migration processes are regulated and characterized by the continuous expression of cell-based surface markers and chemokine receptors. This model enables the generation of synthetic data mimicking flow cytometry measurements as they are frequently obtained within experimental and clinical practice. Our model accounts for marker-driven cell dynamics, enabling the combination of single-cell data analytical methods and mechanistic modeling in order to reveal and quantify the kinetics of marker-driven cell dynamics when applied to experimental measurements. Using our approach, we aim to infer individual cell fate potentials based on specific marker expression profiles, to disentangle the contribution of cell proliferation, differentiation and trafficking to the observed overall responses. This will not only provide insights into the underlying mechanisms regulating immune cell dynamics, but should also pave the way for developing novel therapeutic strategies relying on the modulation of immune responses in various diseases.

Elementary Flux Mode Sampling in Genome Scale Metabolic Networks

Frederik Wieder

Christian-Albrechts-Universität zu Kiel, Germany

Metabolic networks are widely studied in computational biology to predict molecular behavior and understand cellular function. The mass balance and thermodynamic irreversibility constraints for reactions define a polyhedral cone, known as the steady-state flux cone. A key concept to analyze the flux cone in a mathematically and biologically meaningful way are elementary flux modes (EFMs), which provide an inner description of the flux cone through a finite set of generating vectors. However, the number of EFMs grows exponentially with network size, making their full enumeration infeasible for genome-scale models. To address this challenge, several approaches have been proposed to identify subsets of EFMs. Most existing methods are based on solving linear optimization problems (LPs) that yield EFMs as optimal solutions. By blocking subsets of active reactions (i.e. setting $\mathrm{v_i} = 0$) from already known EFMs repeatedly and solving adjusted LPs new EFMs can be determined. In this presentation, we address some of the limitations of LP-based EFM sampling methods and propose strategies to overcome them. Furthermore, we introduce a novel approach that identifies large sets of reactions to block, resulting in significantly smaller LPs that also produce EFMs as optimal solutions but are generally easier to solve. The core idea is to combine a pair of two EFMs e and e' that have already been found and that have oppositely signed flux on one reversible reaction r. By scaling e and e' one can achieve a flux of zero for reaction r in the resulting flux vector v. (mathematically $\mathrm{v} = \lambda\mathrm{e} + \lambda'\mathrm{e}'$ such that $\mathrm{e_r}, \mathrm{e}'_\mathrm{r} \neq 0$ and $\mathrm{v_r} = 0$) By construction, the resulting vector v is a feasible steady-state flux vector. Due to $\mathrm{v_r} = 0$ and $\mathrm{e_r}, \mathrm{e}'_\mathrm{r} \neq 0$, neither e nor e' have inclusionwise smaller support than v. Now v is either a newly found EFM or it is not. In the more likely case that it is no EFM, this is due to its support not being inclusionwise minimal. Therefore a subset of its support is the support of an EFM, which can be found by solving a linear optimization problem where all reactions that are not in the support of v are blocked, leading to a significantly easier LP to be solved. While metabolic reconstructions continue to grow in size and complexity, complete enumeration of EFMs is expected to remain intractable. As a consequence, efficient methods for determining large and unbiased subsets of EFMs are expected to play an increasingly important role in the analysis of genome-scale metabolic networks. With our approach we offer a new method to sample EFMs in large-scale metabolic networks.

Mathematical Modeling of the Aryl Hydrocarbon Receptor Pathway

Vincent Wieland[1,2], Tobias Blum[2], Dilan Pathirana[1,2], Heike Weighardt[2], Irmgard Förster[2], Jan Hasenauer[1,2]

[1]Bonn Center for Mathematical Life Sciences, University of Bonn, Germany; [2]Life and Medical Science Institute, University of Bonn, Germany

The aryl hydrocarbon receptor (AhR) is a ligand-activated transcription factor that orchestrates xenobiotic metabolism via a canonical genomic pathway in which ligand-bound AhR translocates to the nucleus, dimerizes with ARNT, and binds AhR response elements to induce target genes such as Cyp1a1. Despite decades of research it remains unclear which reaction steps differ across ligands and how these differences shape pathway dynamics. We developed a mechanistic, mass-action ordinary differential equation (ODE) model of the canonical AhR pathway spanning extracellular, cytosolic and nuclear compartments. The network includes explicit promoter binding for pCyp1a1 and pAhRR, CYP1A1-mediated intracellular ligand degradation, and transcriptional repression via the AhRR:ARNT complex. We derived analytical steady-state as initial conditions of the system in absence of a ligand. A heteroskedastic error model accounts for amplitude-dependent noise in relative qPCR measurements. Model parameters were estimated by global optimization using multi-start runs on time-course qPCR data for AhRR and Cyp1a1 mRNA in mouse bone-marrow-derived macrophages exposed to three compounds: 3-methylcholanthrene (3MC), indolo[3,2-b]carbazole (ICZ), and bisphenol A (BpA). To interrogate ligand specificity, we conducted an exhasutive model selection evaluating 528 candidate models in which one or two rate constants involving the ligand were allowed to differ between ligands and compared them based on the Akaike information criterion (AIC). Single-ligand calibrations reliably reproduced the dynamics of the experimental data for all three ligands. Although, optimization histories revealed practical non-identifiability of some parameters, parameter-ensemble simulations showed narrow predictive bands for the measured observables, indicating robust predictions. The model selection showed the need for differences in two reactions to explain the qualitative differences between ligands. The top-ranked model (by AIC weight) distinguishes BpA from 3MC and ICZ via (i) altered degradation of the extracellular ligand and (ii) reduced inactivation (off-rate) of promoter-bound pAhRR, consistent with BpA's modulatory, non-classical role in AhR assays. Across near-optimal alternatives—and consistent under AICc/BIC—3MC and ICZ frequently share rate constants, whereas BpA consistently deviates. Clustering of ensemble trajectories across selected models revealed five characteristic dynamical regimes that differ mainly in the timing and magnitude of target gene mRNA. To our knowledge, this is the first mechanistic ODE model that quantitatively captures the genomic AhR pathway with explicit promoter competition and dual feedback, calibrated in macrophages across a classical PAH agonist (3MC), a diet-derived high-affinity agonist (ICZ), and a modulator (BpA). The model recapitulates ligand-specific time courses, identifies a minimal set of reaction steps that must differ to account for BpA's behavior, and yields concrete suggestions for targeted knockout/perturbation experiments. The code is provided in interoperable formats (SBML and PEtab), offering a reproducible starting point for expanding the pathway (e.g., additional ligands, non-genomic crosstalk) and the design of future experiments.

A multi-country comparison of the impact of a potential HIV cure on HIV transmission dynamics

Alfredo De Bellis[1,2,3], Myrthe S. Willemsen[1,4], Jacob Westlund[5], Giorgio Guzzetta[2], Ard van Sighem[6], Kim A. G. J. Romijnders[1], Peter Reiss[7,8,9], Maarten F. Schim van der Loeff[8,9,10], Janneke H. H. M. van de Wijgert[1], Monique Nijhuis[11,12], Mirjam E. E. Kretzschmar[1,4,13], Jan A. C. Hontelez[5,14], Ganna Rozhnova[1,4,15,16]

[1]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands; [2]Center for Health Emergencies, Bruno Kessler Foundation, Trento, Italy; [3]Department of Mathematics, University of Trento, Trento, Italy; [4]Center for Complex Systems Studies (CCSS), Utrecht University, Utrecht, The Netherlands; [5]Department of Public Health, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands; [6]Stichting HIV Monitoring, Amsterdam, The Netherlands; [7]Amsterdam UMC, location University of Amsterdam, Department of Global Health and Infectious Diseases, Amsterdam Institute for Global Health and Development, Amsterdam, The Netherlands; [8]Amsterdam Public Health Research Institute, Global Health and Quality of Care, Amsterdam, The Netherlands; [9]Amsterdam Institute for Immunology and Infectious Diseases, Infectious Diseases Program, Amsterdam, The Netherlands; [10]Department of Infectious Diseases, Public Health Service of Amsterdam, Amsterdam, The Netherlands; [11]Translational Virology, Department of Medical Microbiology, University Medical Center Utrecht, Utrecht, The Netherlands; [12]HIV Pathogenesis Research Unit, Faculty of Health Sciences, University of Witwatersrand, Johannesburg, South Africa; [13]Institute of Epidemiology and Social Medicine, University of Münster, Münster, Germany; [14]Heidelberg Institute of Global Health (HIGH), Medical Faculty and University Hospital, Heidelberg University, Germany; [15]BioISI-Biosystems & Integrative Sciences Institute, Faculty of Sciences, University of Lisbon, Lisbon, Portugal; [16]Faculty of Sciences, University of Lisbon, Lisbon, Portugal

Background & aims of the study: Biomedical research and clinical trials for curative HIV interventions are progressing rapidly, guided by the development of a Target Product Profile (TPP) for an HIV cure. As these efforts advance, it is increasingly important to understand how such interventions could affect HIV transmission dynamics at the population level. To that extent, we aim to explore the importance of cure characteristics across different settings globally. Methods & results: We identified existing population-level HIV models and will invite selected ones to implement an HIV cure based on fitting date, key populations and location, ensuring a representative range of epidemiological dynamics. For each setting, we will systematically assess the impact of four key cure characteristics - clinical efficacy, target population, risk of viral rebound, and risk of reinfection - on HIV incidence and prevalence. As a pilot for the Netherlands, we developed an ordinary differential equations-based mathematical model of HIV transmission among men who have sex with men (MSM), informed by sexual behavior data for this population, and formally calibrated to epidemiological data in the Netherlands between 2017 and 2022. A cure with a 90% uptake and 90% efficacy and no risk of rebound or reinfection reduced the cumulative HIV incidence over ten years up to 60%, compared to a baseline scenario without a cure. In contrast, a cure with a risk of rebound could lead to a remarkable increase in incidence, driven by individuals who experienced viral rebound, even under strict monitoring. Implications: These findings for the Dutch setting underscore the critical role that specific characteristics of curative HIV interventions play in maximizing their public health benefits. Rebound rates that may be considered acceptable at the individual level, such as those outlined in the minimum TPP, may undermine population-level epidemiological progress, even under strict monitoring of cured individuals. In turn, other characteristics, such as the risk of reinfection, may prove more critical in certain settings. This pilot study highlights the importance of aligning cure development with public health goals to ensure that future curative interventions contribute effectively to ending the HIV epidemic globally.

Fitting faster: speeding up parameter fitting in stochastic simulators through variance reduction

Lin Wouters, Johannes Textor[#], Inge Wortel[#]

Radboud University, Nijmegen, The Netherlands

[#]shared last authorship

Motivation: Many studies using computational simulators require some form of parameter fitting where model parameters are chosen to match experimental data. This can be achieved through a process called Simulation Based Inference (SBI), which finds parameters at which the model reproduces experimental data in terms of a chosen outcome metric of interest. Unfortunately, for stochastic simulations this process can be computationally expensive when many simulation runs are needed to get an accurate estimate of the outcome metric at a given parameter set. There is an extensive body of work from the 1980s of theoretically founded variance reduction techniques to obtain accurate outcome estimates with as few replicates as possible.[1] Unfortunately, these methods are overlooked in current SBI research. Here, using a cell motility model as an example, we demonstrate how to apply variance reduction to reduce the required processing power to achieve an accurately fitted stochastic simulator. Methods: We apply the techniques to the Beauchemin Model (BM),[2] a simple cell track simulator that can simulate realistic mean displacement (MD) curves. It can be seen as an extension of a 2-dimensional Random Walk, where the cell changes direction at fixed intervals. The first variance reduction technique we show is Antithetic Sampling,[3] where for every individual simulation, we essentially construct an “opposite” simulation run. We implement this in the BM as follows: given a simulation X_1 with turning angles $\mathrm{a}_1, \mathrm{a}_2, \ldots \mathrm{a}_\mathrm{n}$, we construct a complementary simulation X_2 with turning angles $\mathrm{b}_1, \mathrm{b}_2, \ldots \mathrm{b}_\mathrm{n}$, such that when a_i is large, b_i is small and vice versa. Secondly, we use variance reduction through a control variate,[4] which requires that we have a second outcome metric that correlates with our outcome of interest and for which an analytical solution is known. In the BM, we show that we can apply this technique by using the mean squared displacement (MSD) as a control variate to estimate the MD. Results: The variance reduction in the MD that is achieved by antithetically sampling the turning angles in the BM is minimal (~5% reduction). This does not mean that the technique itself does not work: as expected, the variance in estimates of the average turning angle is reduced to zero. However, the correlation between sampled turning angles and resulting MD is too weak to allow for meaningful reduction of MD variance. This is strongly model-dependent: when we change the way Antithetic Sampling is applied or when we choose a slightly different model or metric, we expect stronger variance reduction. Importantly, even though not every variance reduction method will thus work for every simulation model, we find that when it does work, the impact can be large. An example is applying the control variate method to the BM: As the MSD and MD are strongly correlated, the MSD is a strong control variate for estimating the MD and reduces the variance greatly (~75% reduction). We show that this reduced variance allows us to get better estimates of fitted parameters at the same simulation budget. Discussion: Our work bridges the new field of SBI with long-established work on variance reduction. We find that not all techniques lead to a large variance reduction in every experimental setting. But when a technique is effective, it can massively reduce the number of simulation runs needed to fit model parameters. We expect this to apply for several existing SBI techniques when used to find the posterior mode. We therefore recommend to consider variance reduction for parameter inference of stochastic simulators.

1. Ross S. Simulation (Fifth Edition), Academic Press. 2013. doi:10.1016/C2011-0-04574-X
2. Beauchemin C, Dixit NM, Perelson AS. Characterizing T cell movement within lymph nodes in the absence of antigen. *J Immunol.* 2007;178(9):5505-5512. doi:10.4049/jimmunol.178.9.5505
3. Hammersley JM, Morton KW. A new Monte Carlo technique: antithetic variates. *Math. Proc. Camb. Philos. Soc.* 1956;52(3):449-475. doi:10.1017/S0305004100031455
4. Lavenberg SS, Welch PD. A Perspective on the Use of Control Variables to Increase the Efficiency of Monte Carlo Simulations. *Manage. Sci.* 1981;27(3):322–335. doi:10.1287/mnsc.27.3.322

Intercellular Communication in Plasmodium-infected Liver Tissues: A Spatial Transcriptomics Analyses

Irene Yeboah[1], Aditi Kulkarni[2], Gina Jones[2], Ashley Brauning[2,3], Isabel Mensah[1], Peter Amoako-Yirenkyi[1#], Nana Minkah[2,3#]

[1]Kwame Nkrumah University of Science and Technology, Kumasi, Ghana; [2]Center for Global Infectious Disease Research, Seattle Children's Research Institute, USA; [3]University of Washington, USA

[#]shared last authorship

Introduction: Malaria remains a major global health challenge with 263 million cases and approximately 597,000 deaths reported by the WHO in 2023. Sub-Saharan Africa carries a disproportionately high share of this burden, accounting for 95% of deaths with 76% of deaths in this region occurring in children under the age of five. Infection occurs when a female Anopheles mosquito bites a human and releases Plasmodium sporozoites, which invade hepatocytes (liver cells) and develop into schizonts that rupture into the bloodstream, initiating a blood-stage infection. The infected liver cells release signaling molecules that can influence neighboring uninfected cells, triggering immune responses that may affect disease progression across the liver. Hypothesis: We hypothesize that infection reprograms liver intercellular signaling, leading to infection-specific immune communication pathways that are uniquely activated. Objective: The objective of this work is to model an intercellular cell-cell communication network in Plasmodium-infected liver tissues to identify ligand-receptor signaling pathways that are uniquely activated during infection. Methodology: Our framework uses Nanostring's GeoMx Digital Spatial Profiler (DSP), a novel tissue-based assay for high-plex profiling of protein and RNA within specific regions of interest that provides spatial context in spatial transcriptomics i.e captures the physical location of cells within tissue. GeoMx DSP data from 66 selected regions of interest from adult naive and infected mice tissues were analyzed using a mathematical modeling workflow combining deconvolution, spatial graph construction, and ligand–receptor inference. Cell-type proportions were estimated via a log-normal regression deconvolution algorithm (SpatialDecon) for each region of interest that was selected using Single-cell RNA sequencing data as reference, and a K-nearest neighbor (KNN) cell graph was constructed to model spatial adjacency among inferred cell types. Ligand–receptor co-expression probabilities were computed across graph edges using SpaTalk, yielding intercellular communication scores. Downstream signaling pathways were modeled by integrating KEGG and Reactome databases to trace the propagation from receptor to transcription factor. Results: Deconvolution revealed hepatocytes, endothelial, and Kupffer cell types were dominant in adult naive tissues, while infection induced an increase of monocytes, dendritic subtypes, and innate lymphoid cell types. The cell–cell graph network showed an increased connectivity between Kupffer cells, hepatocytes, and monocytes, suggesting infection intensified immune communication. We found a unique infection-specific signaling in adult liver tissues where monocyte cells acted as sender cells communicating to hepatocytes as receiver cells via Ifnar1, triggering interferon signaling. This finding aligns with existing literature highlighting the role of type I interferon signaling in liver-stage malaria immunity. Their pathway enrichment identified activation of interferon alpha/beta signaling, JAK–STAT, PI3K–Akt, and Toll-like receptor signaling consistent with the hypothesis that infection reprograms liver intercellular signaling toward antiviral and inflammatory states.

Helminth-Induced Immune Training and Its Potential Impact on Tumor Progression

Yixuan Zeng, Wei Liu, Ann-Sophie Mai, Hazel Sahin, Marianne Koschel, Gunther Hartmann, Marc Hübner, Aleksandra Pandyra

Institut für Klinische Chemie und Klinische Pharmakologie, University Hospital Bonn, Germany

Trained immunity, defined as innate immune memory established through epigenetic and metabolic reprogramming, has been implicated in modulating anti-tumor responses. Several training-inducing agents, including BCG and β-glucan, have demonstrated anti-tumor activity, though their effects vary with tumor type and context. Helminths are potent immunomodulators capable of shaping bystander immune responses and imprinting hematopoietic stem and progenitor cells. Despite the well-documented influence of helminths on innate immunity, their potential role in tumor progression remains insufficiently explored. Here, we investigated whether infection with the rodent filarial nematode Litomosoides sigmodontis induces a trained immunity which may impact tumor growth. Mice were infected with L. sigmodontis and evaluated 63 days post infection (dpi), a time point at which adult worms and microfilariae were no longer detectable, indicating resolution of active infection and overt inflammation. Immune profiling by flow cytometry across bone marrow, blood, spleen, lymph nodes, bronchoalveolar lavage, and lung tissue revealed substantial remodeling of both innate and adaptive immune compartments. At 63 dpi, granulocytes ($CD11b^{+}Ly6C^{+}Ly6G^{+}$) were significantly expanded across peripheral lymphoid organs, indicating persistent systemic innate alterations. In lung tissue, naïve and effector $CD4^{+}$ T-cell subsets were both increased. Regulatory T cells ($CD4^{+}CD25^{+}FoxP3^{+}$) were also elevated in lung tissue but unchanged in bronchoalveolar lavage fluid, reflecting a dynamic balance between immune activation and immunoregulation during the post-infection phase. To assess functional consequences for tumor progression, mice were intravenously injected with B16.F10 melanoma cells at 63 dpi. Prior L. sigmodontis infection resulted in prolonged survival trend compared with naïve controls, suggesting that helminth-induced immune imprinting may enhance anti-tumor capacity. Together, these findings indicate that filarial infection induces long-lasting systemic and tissue-specific immune alterations that persist after parasite clearance and may confer a protective phenotype against tumor growth. Future work will test additional tumor models, including leukemia, at different post-infection time points to elucidate mechanisms by which helminth-induced immune training shapes the tumor microenvironment and systemic anti-tumor immunity.

The digital bone marrow niche – A spatio-temporal in silico model of haematopoietic (stem) cells in their bone marrow microenvironment

Osman Abhimata Nugraha, Thomas Zerjatke, Ingmar Glauche, Ingo Roeder

Institute for Medical Informatics and Biometry, TU Dresden, Germany

Haematopoietic stem cell (HSC) maintenance in the bone marrow, including aspects like self-renewal, differentiation, proliferation, and quiescence, critically depends on the local microenvironment, known as the stem cell niche. Dysregulation of this niche is known to contribute to haematological malignancies. However, the spatial complexity of the bone marrow hampers a full understanding of niche-driven HSC regulation and its relation to disease progression. To address this, we are developing a 3D spatio-temporal in silico model based on the Cellular Potts Model (CPM) implemented in Morpheus. In this framework, HSCs and progenitor cells are represented as individual agents whose movements and behaviours evolve in space and time through a combination of deterministic and stochastic rules. These agents interact with each other, with niche components, and with signalling molecules within a particular 3D domain that represents the geometry of the niche (e.g., vasculature). This scaffold can be derived from microscopy data or artificially generated via reaction-diffusion simulations. At the current stage, our model incorporates two reversible HSC states, namely “active” (proliferating) and “inactive” (quiescent), thereby extending a previous model into a spatial context. Preliminary simulations in artificially generated scaffolds demonstrate distinct HSC population dynamics and residence time distributions depending on the scaffold structure. These findings suggest that structural changes in the niche can alter HSC behaviour in the bone marrow and may provide a starting point to better understand aging or disease-related alterations in the microenvironment. We aim to implement an iterative modelling approach in which simulation outputs are continuously compared with experimental observations, and the model is refined accordingly. Through this effort, we hope to advance mechanistic insights into spatial aspects of niche regulation in haematopoiesis and its dysregulation in aging or disease.

Graph Neural Network Surrogates to leverage Mechanistic Expert Knowledge towards Reliable and Immediate Pandemic Response

Agatha Schmidt, Henrik Zunker

German Aerospace Center (DLR), Cologne, Germany

Mechanistic epidemic models have been central to evidence-based decision-making during COVID-19, but time-critical settings limit how much simulation evidence can be assembled before interventions are chosen. We address this bottleneck with a graph neural network (GNN) surrogate for a spatially and demographically resolved mechanistic metapopulation simulator. The surrogate retains the structure and interpretability advantages of the expert model while enabling immediate, web-ready inference. Our design of experiments spans outbreak and persistent-threat regimes, up to three contact change points within the first month, and age-structured (6×6) contact matrices on a 400-node spatial graph (German counties). We benchmark multiple GNN layers—GCN, ARMA, APPNP, and GAT—and identify an ARMAConv-based architecture as offering the best accuracy–runtime trade-off. The ARMAConv model achieves mean absolute percentage errors (MAPE) of 10–27% across 30–90-day horizons and up to three contact changes, with (near) constant runtime independent of forecast length. Compared with the mechanistic simulator, the surrogate accelerates evaluation by factors up to 28,670, allowing responsive “what-if” exploration and straightforward integration into interactive decision-support tools. These results demonstrate how GNN surrogates can translate complex metapopulation models into immediate and reliable operational support for pandemic response