

ISGSB 2026: The 22nd conference on International Study Group for Systems Biology

7–11 September 2026

Ljubljana, Faculty of Computer and Information Science, University of Ljubljana



ISGSB 2026: From Fundamental Insights to Applied Biology
The 22nd conference of the International Study Group for Systems Biology

Ljubljana, Slovenia
September 7 – 11, 2026

Book of Abstracts

Organised by:



ISGSB 2026: The 22nd conference on International Study Group for Systems Biology – Book of Abstracts

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Foreword

Welcome to Ljubljana, and to the 22nd conference of the International Study Group for Systems Biology. Across its long history, the ISGSB has gathered researchers who share a conviction: that to understand life is to understand its systems, the control, kinetics, and thermodynamics that turn molecular mechanism into cellular function. That idea runs through this year's programme, which connects fundamental systems biology with its reach into medicine, plant science, and industrial biotechnology.

This volume collects the 73 contributions accepted for the conference, 47 talks across twelve thematic sessions and 26 posters, from 254 researchers working in nineteen countries on four continents. Their work moves from the theory and dynamics of metabolic modelling to multi-omics and cancer, from microbial communities and plant stress to the shared tools and standards that keep systems biology reproducible and open.

We hope this book will guide you through the days ahead and, afterwards, stand as a record of the science exchanged here. Welcome to ISGSB 2026.

The Organising Committee
Ljubljana, September 2026

Committees

Scientific Committee

- Dr. Carissa Bleker, National Institute of Biology
- Prof. FJ Bruggeman, Vrije Universiteit Amsterdam
- Dr. Ronan Fleming, University of Galway
- Dr. John Hancock, University of Ljubljana
- Prof. Ines Heiland, UiT The Arctic University of Norway
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- Dr. Anže Županič, National Institute of Biology

Organising Committee

- Dr. Carissa Bleker, National Institute of Biology
- Ana Halužan Vasle, University of Ljubljana
- Dr. John Hancock, University of Ljubljana
- Prof. Miha Moškon, University of Ljubljana
- Sergej Praček, National Institute of Biology
- Dr. Anže Županič, National Institute of Biology

Acknowledgements

The conference is organised by the National Institute of Biology and the University of Ljubljana, Faculty of Computer and Information Science, and is held with the generous support of Acies Bio, Ljubljana Tourism and Omega.

We thank the Scientific Committee for reviewing the submissions, the session chairs for guiding the programme, and every author and presenter whose work fills this volume.

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Programme

Monday, 7 September | 10:00–16:00 | YISGSB

Ice breaking activity (YISGSB)

Science Communication Workshop (YISGSB)

PowerPoint Karaoke (YISGSB)

Rožnik walk (YISGSB)

Monday, 7 September | 12:30–14:00 | Lunch

Monday, 7 September | 17:30–18:30

Registration (Auditorium)

Monday, 7 September | 18:30–21:00

Welcome reception (Auditorium)

Tuesday, 8 September | 08:30–10:00

Theory and dynamics of metabolic modelling (Part 1) (Main hall)

Chaired by: Ines Heiland

- | | |
|--------------------|--|
| 08:30–08:50 | Functional consequences of the autocatalytic structure of glycolysis: energy-status homeostasis and flux maximization (<i>Luis A. Salinas-Te</i>) |
| O1 | |
| 08:50–09:10 | Metabolomics and fluxomics in ex vivo precision-cut liver slices of Glycogen Storage Disease type I (<i>Esther Homan</i>) |
| O2 | |
| 09:10–09:30 | The role of fatty acid oxidation during combined fasting and acute cold stress: Metabolic reprogramming of glucose and lipid metabolism (<i>Anette Haak</i>) |
| O3 | |
| 09:30–09:50 | Exploring new venues in single-molecule transcriptomics with the SQANTIverse (<i>Ana Victoria Conesa Cegarra</i>) |
| O4 | |

Tuesday, 8 September | 10:00–10:30 | Coffee break

Tuesday, 8 September | 10:30–12:30

Mechanistic modelling meets multi-omics: Towards personalised and predictive systems biology (Main hall)

Chaired by: Anu Raghunathan

- | | |
|--------------------|---|
| 10:30–10:50 | Expanding enzyme-constrained metabolic modelling to human systems: A Julia-based pipeline demonstrates high predictive power (<i>Hugues Escoffier</i>) |
| O5 | |
| 10:50–11:10 | Investigating <i>P. falciparum</i> metabolism by integrating quantitative biochemical analysis and Genome Scale Metabolic modelling (<i>Tasmin Summerton</i>) |
| O6 | |
| 11:10–11:30 | Physiologically relevant Multi-Omics Flux Analysis Reveals Metabolic Mechanisms of drug-Induced Liver Toxicity (<i>Zita Soons</i>) |
| O7 | |

11:30–11:50 O8	Signal propagation on causal fish knowledge network for proliferation (<i>Miha Tome</i>)
11:50–12:10 O9	Mathematical Modelling of the Impact of Age and Sex Steroids on Female Blood Pressure Regulation (<i>Elena Katharina Heinze</i>)
12:10–12:30 O10	Strategies for the use of Universal Differential Equations to advance Personalised Medicine. (<i>Shauna O'Donovan</i>)

Tuesday, 8 September | 12:30–14:00 | Lunch

Tuesday, 8 September | 14:00–15:30

Computational models for plant growth, stress, and interactions (Main hall)

Chaired by: Anna Matuszyńska

14:00–14:20 O11	Investigating the principles of plant growth-defence trade-offs in biotic interactions using metabolic modelling (<i>Jan Zrimec</i>)
14:20–14:40 O12	Inference of growth and division kinetics in a population balance model of <i>Chlamydomonas reinhardtii</i> with Gaussian process regression (<i>Steffen Waldherr</i>)
14:40–15:00 O13	A metabolic model of the leaf-associated bacterium <i>Paraburkholderia dioscareae</i> links the ethylene precursor ACC to core carbon pathways (<i>Pablo Rolle</i>)
15:00–15:20 O14	A systems-level framework for mapping plant heat-stress memory into dynamic regulatory state-space (<i>El Hadji Malick Cisse</i>)

Tuesday, 8 September | 15:30–15:50

Poster Slam 1 (Main hall)

Tuesday, 8 September | 16:00–18:00 | Poster session and beer tasting

Poster session 1 (Auditorium)

P1	Predicting hepatotoxic metabolites in drug metabolism (<i>Hester Chapman</i>)
P2	Oxygen-dependent restructuring of circadian sterol biosynthesis in HepG2 cells revealed by generalised CosinorPy modelling of LC/MS-MS time-series data (<i>Katarina Nahtigal</i>)
P3	Investigating the Reversibility of Rubisco's Catalytic Mechanism and Its Implications for Carbon Fixation Models (<i>Yuval Goobes</i>)
P4	Analysing energy dissipation partitioning in different environmental conditions with the help of a mechanistic model of proton-motive force (<i>Joshua Ebeling</i>)
P5	Explainable graph neural networks for condition-specific gene expression analysis and link prediction in Arabidopsis (<i>Klara Šuštar</i>)
P6	Potatoes local Ca ²⁺ signalling in space and time (<i>Sergej Praček</i>)
P7	Bioelements: A tool to investigate biological phenomena in 2D (<i>Tim Nies</i>)
P8	Spatial transcriptomics analysis of complex skeletal muscle architecture (<i>Irma Zeljković</i>)
P9	Cellular Economics of Exchanged Metabolites Alter Ratios of Microbial Trading Partners in Predictable Manner (<i>Ross Carlson</i>)
P10	Towards a Reproducible Thermodynamic Model of E. coli Gene Regulatory Network for the In-Silico Design of Unconventional Computing Platforms (<i>Ana Halužan Vasle</i>)
P11	A multi-meta-omics study of microbial metabolic potential and its manifestations in marine microbial communities (<i>Pranas Grigaitis</i>)

Wednesday, 9 September | 08:30–10:00

Metabolic modelling and multi-omics approaches in cancer research (Main hall)

Chaired by: Miha Moškon

- 08:30–08:50 Constraints-based metabolic modelling identifies ME2–ME3 synthetic lethality
O15 in temozolomide-resistant glioblastoma (*Anu Raghunathan*)
- 08:50–09:10 Analysing tumour heterogeneity using scRNA-seq data and genome-scale
O16 metabolic models (*Ida Zeljković*)
- 09:10–09:30 Integrated Multi-Omics and Flux Analysis Reveal Cell-State-Dependent
O17 Metabolic Responses to Dichloroacetate in Melanoma (*Mingjia Zhang*)
- 09:30–09:50 Transcriptome-driven constraint-based modelling reveals metabolic targets for
O18 ovarian cancer (*Kate Meeson*)

Wednesday, 9 September | 10:00–10:30 | Coffee break

Wednesday, 9 September | 10:30–12:30

Refining and engineering the predictive blueprint of microbial cells (Main hall)

Chaired by: Anže Županič

- 10:30–10:50 Cell Geometry and Membrane Protein Crowding Constrain Escherichia coli
O19 Growth Rate, Overflow Metabolism, Respiration, and Maintenance Energy.
(*Ross Carlson*)
- 10:50–11:10 Thermodynamics of Microbial Growth under nutrient limitation (*Oliver Ebenhöf*)
O20
- 11:10–11:30 Are Computational Predictions of Essential Genes as precise as Experiments?
O21 (*Pareena Verma*)
- 11:30–11:50 Generation of metabolomic-informed models of metabolism in complex microbial
O22 communities (*Coralie Muller*)
- 11:50–12:10 Metabolic modeling of fungal pathogens – Gains and limitations (*Sascha Schäub*-
O23 *le*)
- 12:10–12:30 The art of phenotype design: unlocking StrainDesign for complex substrate uti-
O24 lization (*Maaïke Remeijer*)

Wednesday, 9 September | 12:30–14:00 | Lunch

Wednesday, 9 September | 14:00–15:30

Theory and dynamics of metabolic modelling (Part 2) (Main hall)

Chaired by: Johann Rohwer

- 14:00–14:20 Use of non-autonomous differential equations in modelling metabolic processes
O25 (*Stefan Schuster*)
- 14:20–14:40 The dynamic world of metabolic cofactors (*Ines Heiland*)
O26
- 14:40–15:00 From large networks to large dynamic models: the steps and missteps of going
O27 big (*Anže Županič*)
- 15:00–15:20 Model Refinement of Partially Specified Boolean Networks Using Phenotype Con-
O28 trol (*David Safranek*)

Wednesday, 9 September | 15:30–15:50

Poster Slam 2 (Main hall)

Wednesday, 9 September | 16:00–18:00 | Poster session and wine tasting

Poster session 2 (Auditorium)

- P12 NAViFluX: A Visualization-Centric Workbench for Interactive Analysis, Refinement, and Design of Genome-Scale Metabolic Networks (*Manjunatha B K*)
- P13 Thermodynamic energy constraints shape enzyme sequence and active-site geometry: evidence from methanogenic archaea across the energetic spectrum of life (*Tamir Yerushalmi*)
- P14 Modular response analysis reveals distributed control of insulin sensitivity in C2C12 skeletal muscle cells. (*Klarissa Shaw*)
- P15 Reconstruction of context-specific genome-scale metabolic models of mammalian cells: development of a robust protocol (*Tadeja Režen*)
- P16 pyPGLM, a toolbox for the fast contextualization of logical networks (*Sébastien De Landtsheer*)
- P17 A digital tomato: modelling resource allocation in young growing fruit (*Chloé Ladreyt*)
- P18 Development of an interactive web application for constraint based modelling (*Zuhtu Tutar*)
- P19 Subtype-Specific Gene Expression and Proliferation Dynamics in 2D and 3D High-Grade Serous Ovarian Cancer Cell Cultures (*Lana Černigoj*)
- P20 Investigating metabolic reprogramming in pancreatic ductal adenocarcinoma using genome-scale metabolic modelling (*Filip Petrovič*)
- P21 The role of fungal LysM effectors in plant immunity suppression and microbiota manipulation (*Flora Schlüter*)
- P22 ANCHORS - Attention-based Neural Computation and Hybrid model Optimization for Reconstruction of Complex Dynamic Biological Systems (*Žiga Pušnik*)
- P23 Metabolic-isotopic model of sulfite reduction: Environmental and evolutionary implications (*Maayan Kaneti*)
- P24 Integration of omics data for response prediction to neoadjuvant treatment in resectable Non-Small Cell Lung Cancer (*Egils Stalidzans*)
- P25 TRIM-Flux: Integrating Metabolic Flux into Multimodal VAEs for Predicting T-cell State Transitions in Cancer Immunotherapy (*Aljaž Kos*)
- P26 Using the ReStoRunT idea to document provenance in transformation of large, complex Excel workbooks (*Wolfgang Müller*)

Thursday, 10 September | 08:30–10:00

Metabolic cross-feeding and inter-species dynamics (Main hall)

Chaired by: Frank Bruggeman

- 08:30–08:50 O29 Metabolic games in an autotroph-heterotroph consortium: eco-evolutionary analysis of cooperative, private and cheater exoenzyme strategies (*Tanvir Hassan*)
- 08:50–09:10 O30 Fermentation revisited: facultative anaerobes and the rate-yield trade-off in the gut microbiome (*Johannes Zimmermann*)
- 09:10–09:30 O31 Butyrate production is shaped by microbial interactions in an infant synthetic community (*Coen Berns*)
- 09:30–09:50 O32 Optimizing the resource allocation between biochemical defence and counter-counter defence in pathogenic and trophic interactions. Steady-state analysis (*Lukas Korn*)

Thursday, 10 September | 10:00–10:30 | Coffee break

Thursday, 10 September | 10:30–12:30

Bridging omics and metabolic models (Main hall)

Chaired by: John Hancock

10:30–10:50 O33	COBRA-k: a novel framework bridging constraint-based and kinetic metabolic modeling (<i>Steffen Klamt</i>)
10:50–11:10 O34	ThermoDB – Metabolic Potentials Under User-Defined Conditions (<i>Johann Rohwer</i>)
11:10–11:30 O35	From RNA-Seq to Mechanistic Insights: A Unified Pipeline for Context-Specific Metabolic Model Analysis (<i>Vanille Lejal</i>)
11:30–11:50 O36	scFASTCORMICS 2.0: Fast and Scalable Context-Specific Metabolic Modeling from Single-Cell RNA-seq Data of the Tumor Microenvironment (<i>Evelyn Gonzalez</i>)
11:50–12:10 O37	Functional tracer proteo-metabolomics: a toolbox to study cellular metabolism and protein modification dynamics (<i>Marcel Kwiatkowski</i>)
12:10–12:30 O38	Developing Approaches for Knowledge-Driven Protein 3D Structure Prediction: Next Steps Beyond AI (<i>Yazan Haddad</i>)

Thursday, 10 September | 12:30–14:00 | Lunch

Thursday, 10 September | 13:30–14:30

ISGSB Board meeting (Main hall)

Thursday, 10 September | 13:30–15:30

Session 1 (ELIXIR) (ELIXIR community hybrid meeting)

Thursday, 10 September | 15:00–18:00

Excursion (historic city tour or hike) (Satellite Event)

Thursday, 10 September | 16:00–18:00

Session 2 (ELIXIR) (ELIXIR community hybrid meeting)

Thursday, 10 September | 19:30–22:30

Conference dinner (Pivnica Union) (Satellite Event)

Friday, 11 September | 08:30–10:00

Systems biology communities & services (Main hall)

Chaired by: Carissa Bleker

08:30–08:50 O39	The ELIXIR Systems Biology Community and Advancing FAIR and Trustworthy Systems Biology: From Principles to AI-Enhanced Practice (<i>John Hancock</i>)
08:50–09:10 O40	Improving Accessibility, Curation and Reusability of Enzyme Kinetic Data in SABIO-RK (<i>Ulrike Wittig</i>)
09:10–09:30 O41	Interfacing systems biology diagrams and Large Language Models with the MIN-ERVA Platform (<i>Marek Ostaszewski</i>)

Friday, 11 September | 08:30–10:00

Friday, 11 September | 10:00–10:30 | Coffee break

Friday, 11 September | 10:30–12:30

Theory and dynamics of metabolic modelling (Part 3) (Main hall)

Chaired by: Stefan Schuster

- 10:30–10:50 Oscillatory wave propagation in yeast and -cell populations (*Jacky Snoep*)
[O42](#)
- 10:50–11:10 Quantitative Phasor Analysis of Biological Oscillators (*Dawie van Niekerk*)
[O43](#)
- 11:10–11:30 Age-based approach to characterize the dynamics of cellular processes (*Elad Noor*)
[O44](#)
- 11:30–11:50 Clostridial acidogenesis product profiles are discontinuous: a thermodynamic hypothesis (*Christoff Odendaal*)
[O45](#)
- 11:50–12:10 Making sense of time series with universal differential equations (*Marvin van Aalst*)
[O46](#)
- 12:10–12:30 FASTERCC: Accelerating Flux Consistency Testing and Context-Specific Reconstruction for Large-Scale Metabolic Network Models (*Evelyn Gonzalez*)
[O47](#)

Friday, 11 September | 10:30–12:30

Session 4 (ELIXIR) (ELIXIR community hybrid meeting)

Friday, 11 September | 12:30–13:30 | Lunch

Abstracts

Theory and dynamics of metabolic modelling (Part 1)

Chaired by: Ines Heiland

O1

Functional consequences of the autocatalytic structure of glycolysis: energy-status homeostasis and flux maximization

Luis A. Salinas-Te¹, Frank Bruggeman¹, Jacky Snoep², Bas Teusink¹

¹VU Amsterdam, Amsterdam, NL

²Stellenbosch University, Stellenbosch, ZA

Oral presentation

Glycolysis ranks amongst the most prevalent catabolic pathways on our planet. Although variants of it exist, glycolysis is always autocatalytic: ATP is invested in upper glycolysis and a net surplus is made in lower glycolysis. As a result, upper-glycolysis kinases have ATP as a substrate while lower-glycolysis kinases have ADP as substrate instead. This implies that the glycolytic flux is zero when either the ATP or ADP concentration is zero and that the glycolytic flux reaches a maximum as a function of the ATP over ADP ratio, a measure of the energy status of a living cell. Here we discuss the consequences of these universal features of glycolysis for flux maximisation and homeostasis of the cellular energy status.

Keywords: Glycolysis, homeostasis, Autocatalytic pathway

O2

Metabolomics and fluxomics in ex vivo precision-cut liver slices of Glycogen Storage Disease type I

Esther Homan¹, Martijn Rutten¹, Kishore Krishnamurthy¹, Candelas Gross Valle¹, Albert Gerding¹, Miriam Makkinje¹, Pim de Blaauw², Trijnie Bos², Peter Olinga³, Bart van de Sluis², Terry Derks¹, Justina Wolters¹, Maaike Oosterveer^{2,4}, Rebecca Heiner-Fokkema², Barbara Bakker¹

¹University Medical Center Groningen, Groningen, Netherlands

²University Medical Center Groningen, Netherlands

³University of Groningen, Netherlands

⁴Radboud University Medical Center, Netherlands

Oral presentation

Glycogen Storage Disease type I (GSDI) is a rare, autosomal-recessive inherited metabolic disease. GSD type Ia (GSDIa) is caused by a deficiency of glucose-6-phosphatase (encoded by the G6PC1 gene) and type Ib (GSDIb) by a deficiency of glucose-6-phosphate translocase (G6PT). The mechanisms behind the relation between aberrant metabolism and the development of long-term complications in GSDI patients, including hepatocellular adenoma and carcinoma, are unknown. Beyond GSDI, altered fluxes of glucose-6-phosphate into glycogen, lipids and lactate have been quantitatively documented in GSDI patients and preclinical models. Elevated lactate production and upregulated glycogen metabolism have been seen in several tumour types. However, glucose-6-phosphate can spill over into many more metabolic pathways; the glycolysis, the pentose phosphate pathway, the TCA cycle, the one-carbon and NAD⁺ metabolism. As a first and important step, this project aims to comprehensively and quantitatively analyse the overflow metabolism in preclinical models of GSDI. To investigate this, we performed a stable-isotope-based fluxomics study in hepatic GSDI vs WT precision-cut liver slices (PCLS). PCLS still closely resemble in vivo liver tissue, while allowing detailed dynamic analysis and multiple interventions on slices from a single mouse liver. Stable-isotope-labelled precursor [13C3]-glycerol was supplied to PCLS of WT mice over time, in the absence/presence of S4048. S4048 inhibits G6PT, thereby

mimicking acute GSDIb. Isotopic enrichment of metabolites was measured by Gass Chromatography(-Tandem) Mass Spectrometry. Our results showed that glucose production was decreased after addition of S4048, while lactate increased following [13C3]-glycerol supplementation. Incubation of PCLS with [13C3]-glycerol showed an increase of M+3 lactate of ~15% without S4048 and ~30% in the presence of S4048 after 72h of incubation (n=3). Additionally, incubation with [13C3]-glycerol showed an increase of dihydroxyacetone phosphate (M+3) after addition of S4048 after 3h of incubation. Other gluconeogenic metabolites showed no changes in this timeframe. Furthermore, citrate showed an increased M+2 enrichment of ~15% in the presence of S4048 after 48h of incubation. The concentration remained constant between groups. Similar results were seen for aspartate (M+3), malate and -ketoglutarate (M+2). To conclude, TCA cycle intermediate enrichment is altered in GSDIb PCLS. Interestingly, TCA flux alterations are suggested but not proven in GSDIb. Future research of NAD+ and one carbon metabolic fluxes is ongoing in hepatocyte-specific genetic GSDI mice. Insights into GSDI overflow fluxes might eventually be used to gain insight into the relationship between aberrant metabolism and tumour development in GSDI patients.

Keywords: Glycogen storage disease type I, Glucose-6-phosphate metabolism, Stable-isotope based fluxomics , Precision-cut liver slices, TCA cycle alterations

O3

The role of fatty acid oxidation during combined fasting and acute cold stress: Metabolic reprogramming of glucose and lipid metabolism

Anette Haak¹, Ligia Akemi Kiyuna¹, Anne-Claire M. F. Martines¹, Wenxuan Zhang¹, Albert Gerding¹, Miriam Makkinje¹, Niels Kloosterhuis¹, Marieke Smit¹, Rick Havinga¹, Maaïke Goris¹, Marcel de Vries¹, Mirjam H. Koster¹, Laura Bongiovanni², Alain de Bruin², Rob H. Henning¹, Rainer Bischoff³, Terry Derks¹, Justina Wolters¹, Maaïke H. Oosterveer¹, Dirk-Jan Reijngoud³, Barbara Bakker¹

¹University Medical Center Groningen, Groningen, Netherlands

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Oral presentation

Conditions of increased energetic demand, such as fasting and cold exposure, raise the reliance of the whole-body metabolism on mitochondrial fatty acid oxidation (mFAO). Defects in mFAO frequently cause life-threatening hypoglycemia under these conditions, yet the underlying mechanisms remain unclear. Here, we investigated systemic adaptations in glucose and lipid metabolism during pronounced energetic stress, using a mouse model of medium-chain acyl-CoA dehydrogenase deficiency (MCADD), the most prevalent mFAO disorder. By integrating analyses across liver and peripheral tissues, we aimed to determine whether peripheral fuel switching from fatty acids to glucose contributes to hypoglycemia onset and to characterize compensatory metabolic responses during metabolic decompensation. Combined fasting and acute cold exposure induced significantly lower glucose and ketone body levels in MCAD-knockout (MCAD-KO) mice compared to their WT counterparts. In separate experiments, [14C]-palmitoylcarnitine or [14C]-deoxyglucose uptake into peripheral tissues were assessed, showing that, irrespective of genotype, most tissues of cold-exposed mice exhibited decreased [14C]-palmitoylcarnitine-derived metabolite retention, which was partially abolished in liver, skeletal and cardiac muscle following MCAD loss. In contrast, glucose uptake upon cold exposure remained largely unchanged, except in brown adipose tissue (BAT) and brain compared to 25°C. At 4°C, MCAD-KO mice exhibited reduced hepatic amino acid levels and increased plasma acylcarnitine concentrations, while hepatic acylcarnitine homeostasis was preserved compared to WT. No changes in hepatic TCA cycle intermediate abundances in cold-exposed MCAD-KO mice relative to WT were found. Untargeted lipidomics analysis revealed an accumulation of triglyceride species containing medium-length acyl-chains in liver and BAT of cold-exposed MCAD-KO mice, relative to WT. In conclusion, hypoglycemia in energetically challenged MCAD-KO mice was not attributable to increased peripheral glucose consumption. However, our results corroborate the central role of liver mFAO in glucose homeostasis during cold stress and reveal a compensatory response in which amino acids substitute for

fatty acids as substrate for glucose, ketone bodies and ATP synthesis, while excess medium-chain fatty acid intermediates are exported into plasma or rerouted into triglyceride synthesis to mitigate toxic metabolite accumulation and potentially coenzyme A sequestration in liver.

Keywords: Mitochondrial fatty acid oxidation disorders, MCAD deficiency, Acute cold exposure, Hypoglycemia, Systems Medicine

O4

Exploring new venues in single-molecule transcriptomics with the SQANTIverse

Ana Victoria Conesa Cegarra

Spanish National Research Council, Valencia, ES

Oral presentation

Long-read sequencing (LRS) technologies have become robust alternatives to short-read methods for a wide range of applications. Over the last five years, platforms such as Oxford Nanopore and Pacific Biosciences have made significant advancements in accuracy and throughput, positioning themselves as practical options alongside Illumina RNA-seq for transcriptomics research. Our lab has been at the forefront of this progress, developing SQANTI, a widely adopted tool for quality assessment and quantification of long-read transcript models. However, with the evolution of LRS technologies, there is a growing demand for complementary algorithms tailored to transcriptomics. These include accurate identification and quantification of transcripts, correction of technological biases, optimization of experimental designs for large-scale studies, creation of benchmarking resources, data visualization tools, and functional annotation of full-length transcript variants. I will present the expanded suite of SQANTI tools, designed to comprehensively address these challenges. For benchmarking, SQANTI-SIM stands out as it simulates long-read and orthogonal data with precise control over transcript novelty, enabling robust evaluations of both annotated and novel transcript detection. The BUGSI framework offers a set of universal single-isoform genes, serving as internal standards to identify RNA degradation and library preparation issues. SQANTI-reads provides a critical evaluation of raw data quality in multi-sample experiments, identifying outliers and technological biases while ensuring data quality standards for discovery are met. SQANTI3 evaluates transcript reconstruction algorithms, aiding in the accurate identification of transcript models from long-read data. Modules such as Filter, Rescue, and Requant refine transcript models, enhancing transcriptome quality and precision in quantification. Our research highlights distinct quantification biases in lrrNA-seq compared to short-read RNA-seq, underscoring the need for specialized normalization approaches. I will also explore alternative methods for defining joint transcriptomes in multi-sample experiments and their implications for transcript detection. Finally, I will introduce IsoAnnot, now incorporated into the SQANTI suite, which differentiates productive from unproductive transcripts and provides functional labels to deepen our understanding of the biological roles of alternative splicing.

Keywords: Long-read transcriptomics, SQANTIverse, data analysis, software development

Mechanistic modelling meets multi-omics: Towards personalised and predictive systems biology

Chaired by: Anu Raghunathan

O5

Expanding enzyme-constrained metabolic modelling to human systems: A Julia-based pipeline demonstrates high predictive power

Hugues Escoffier¹, Thomas Sauter²

¹University of Luxembourg, Esch-Alzette, Luxembourg

²University of Luxembourg, Belvaux, Luxembourg

Oral presentation

Enzyme-constrained genome-scale metabolic models (ecGEMs) improve phenotype and flux predictions by integrating enzymatic turnover numbers (kcat), thereby introducing quantitative limits on reactions capacities and substantially reducing the feasible flux space. Despite their success [1-3], particularly in *Saccharomyces cerevisiae* [4], broader application of ec-GEMs remains a major challenge. These limitations become especially apparent in the case of human reconstructions, where increased model complexity, sparse kinetic data, and the requirement for context-specific constraints complicate the large-scale application of ec-GEMs.

To address these limitations, we present a modular workflow enabling construction of human ec-GEMs. The workflow combines WILDkCAT, a Python package for automated kcat retrieval from BRENDA [5] and SABIO-RK [6] databases, with COBREXA.jl, a high-performance constraint-based modelling framework in Julia [3]. A central contribution of this work is the construction of a context-specific enzyme-constrained model, achieved by integrating quantitative proteomic data as capacity constraints, transforming the model from a qualitative representation into a quantitative, biologically grounded predictive tool. All steps, from kcat retrieval and data processing to model reconstruction and analysis, are fully documented and require minimal custom code, ensuring reproducibility and straightforward adaptation to specific cell types, tissues, or growth conditions.

We validated the pipeline on the MCF7 breast cancer cell line as a representative and well-characterised human system. The reconstructed enzyme-constrained context-specific model significantly improved predictions, particularly regarding uptakes and secretion fluxes, which closely match experimentally measured exchange rates. Validation extends to intracellular flux distributions, with the predicted fluxes for glycolysis and the pentose phosphate pathway being consistent with isotope labelling data.

Taken together, this work establishes a foundation for human ec-GEM modelling. By removing key technical barriers, such as automated kcat retrieval and integration of proteomic constraints into large-scale reconstructions, the pipeline opens the door to broader applications: systematic investigation of metabolic reprogramming across cancer cell lines, multi-omics data integration, and patient-specific metabolic modelling. This represents a significant step toward making enzyme-constraint-based modelling a standard tool in systems medicine, extending a framework that has proven game-changing in microbiology to the field of human biology.

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Keywords: Metabolic Modelling, Enzyme constraint, Julia, Human metabolism , Proteomics

O6

Investigating *P. falciparum* metabolism by integrating quantitative biochemical analysis and Genome Scale Metabolic modelling

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Oral presentation

Plasmodium falciparum relies heavily on the human host for essential nutrients for intraerythrocytic growth, the driver of clinical malaria. As the parasite matures within the red blood cell, it consumes host resources and adapts its metabolic priorities. Since this metabolic adaptation varies across the parasite’s life cycle, stage-specific metabolism produces distinct biochemical profiles in both the infected RBC and the external environment. The parasite’s essential metabolic pathways, including glycolysis and amino acid metabolism, result in external metabolite fluxes that reflect infection severity, and accelerated parasite metabolism could contribute to severe pathologies such as lactic acidosis and hypoglycemia.

In this study, we apply a stage-specific framework to quantify fluxomic profiles throughout the parasite’s

developmental cycle, accounting for the non-linear nature of its metabolic activity. We integrated in vitro experimental data into a curated genome-scale metabolic model (GEM) of *P. falciparum*. Our simulations demonstrate that while the parasite excretes most hemoglobin-derived amino acids and lactate, it selectively scavenges specific amino acids and glucose from the host environment. These predictions are consistent with our in vitro data and supported by published clinical flux measurements in patient plasma. By extending the model to better reflect in vitro biological conditions, we present a refined GEM capable of predicting stage- and strain-specific druggable targets, optimizing growth conditions for mutant cell lines, and streamlining screening for antimalarial combination therapies.

Keywords: genome-scale metabolic modelling , *Plasmodium falciparum* , haemoglobin degradation, targeted metabolomics , amino acid flux

O7

Physiologically relevant Multi-Omics Flux Analysis Reveals Metabolic Mechanisms of drug-Induced Liver Toxicity

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Oral presentation

Adverse drug events remain a major challenge in drug development and clinical practice, partly because conventional preclinical assays fail to reproduce dynamic human drug exposure and because biomarkers for drug-induced liver injury (DILI) typically reflect damage that has already occurred rather than early adaptive responses. Within the EU HeCaToS project [1], we developed a systems pharmacology framework integrating physiologically based pharmacokinetic (PBPK) modeling with multi-omics profiling of primary human liver spheroids exposed to clinically relevant drug concentration trajectories. Using the anti-tuberculosis drug isoniazid as a case study, we combined time-resolved transcriptomics, proteomics, metabolite exchange measurements, viability data, and lipid availability from cell death with genome-scale metabolic modeling to resolve pathway-level adaptations under therapeutic and toxic exposure. Context-specific models were reconstructed using DEXOM/iMAT-related workflows [2], enabling exploration of alternative metabolic states under constraints. Integrated analyses revealed partially orthogonal regulation at transcriptomic and proteomic levels. Proteins showed substantial variation (mean correlation 0.84 ± 0.04), whereas transcripts were globally stable (0.998 ± 0.001) but still contributed to the dominant variation axis. Proteomics correlated more strongly with predicted flux changes than transcriptomics ($r = 0.19$ vs. 0.016), particularly in lipid metabolism. Flux analysis identified the tricarboxylic acid cycle as a central hub linking amino acid catabolism, lipid metabolism, mitochondrial energy production, and redox balance under toxic stress. Increased amino acid utilization and rerouting of central carbon and nitrogen metabolism preceded apoptosis, indicating early metabolic adaptation. Lipid availability from cell death was several orders of magnitude lower than amino acid availability, confirming active metabolic reprogramming rather than passive release from dying cells. Toxic exposure induced a lipid-dominated state characterized by enhanced β -oxidation, cholesterol turnover, phospholipid remodeling, increased glutathione demand, and altered bile acid metabolism, whereas therapeutic exposure maintained metabolic flexibility and bile acid synthesis. To assess clinical relevance, we analyzed real-world data from the Explorys database [3], where isoniazid treatment was associated with changes in classical liver injury markers and variability in glucose and urea levels, consistent with model-predicted alterations in central carbon and nitrogen metabolism. Together, this PBPK-informed multi-omics framework demonstrates how mechanistic metabolic modeling reveals early functional adaptations not apparent from expression data alone. The approach provides a generalizable strategy for integrating systems pharmacology, omics data, and constraint-based modeling to improve mechanistic understanding, early detection, and safety assessment in DILI research.

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Keywords: metabolic flux analysis, liver toxicity, drugs, proteomics, transcriptomics

O8

Signal propagation on causal fish knowledge network for proliferation

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Oral presentation

Chemicals with diverse structures and mechanisms of action can converge on the same phenotypic outcome — reduced cell proliferation and impaired fish growth. Using a gill-derived rainbow trout (*Oncorhynchus mykiss*) epithelial cell line (RTgill-W1), we have previously demonstrated that suppression of cell population growth in vitro reliably predicts growth inhibition in vivo, and that this phenotype is shared across structurally unrelated compounds. The central mechanistic question is therefore: which molecular nodes and pathways are consistently perturbed across chemicals to produce this common outcome?

To address this, we constructed a large-scale causal biological network in Neo4j by integrating KEGG metabolic and signalling pathways and CausalBio signalling models through manual curation. The network spans three levels of biological organisation — from individual molecular entities (genes, compounds, complexes) through signed, directed molecular interactions, to a meta-level pathway overview — providing both a mechanistically propagation substrate and an interpretable summary layer. RNA-seq and RIBO-seq data from RTgill-W1 cells exposed to five chemicals (propiconazole, trifloxystrobin, tebuthiuron, methimazole, and 2-mercaptobenzothiazole) at three time-points versus an untreated control were aggregated to network nodes using FDR-weighted mean log fold-changes and propagated using Random Walk with Restart with edge sign semantics. Both omics layers were analysed independently to distinguish transcriptional from translational perturbation.

As expected, cell cycle signalling nodes ranked among the most perturbed across all chemicals, consistently in both individual differential analysis and network propagation of RNA-seq and RIBO-seq data. Contrary to our expectations, this effect was not restricted to later timepoints — a strong response was already evident on day one, with more chemical-specific patterns emerging subsequently. Among the most prominent pathways, we identified xenobiotic metabolism response, mTOR signalling, and p53 signalling, suggesting convergent upstream sources of the perturbation signal. In terms of metabolism, lipid-related pathways, particularly steroid and sphingolipid metabolism, showed the earliest shifts. This rapid, cross-chemical convergence on cell cycle suppression points to an early conserved cellular stress response, whose mechanistic architecture and connection to baseline toxicity warrant further investigation.

Keywords: Knowledge network, Signal propagation, Proliferation, Ecotoxicology, RIBO-seq

O9

Mathematical Modelling of the Impact of Age and Sex Steroids on Female Blood Pressure Regulation

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Oral presentation

Hypertension is among the main risk factors for cardiovascular disease. Disease progression and treatment are highly individual and sex-specific. Despite the cardioprotective effect of endogenous steroid

hormones such as estradiol (E2), few studies investigate menstrual cycle phase-dependent blood pressure differences in direct relation to steroid hormone levels, and the ones that exist often arrive at inconsistent results.

To aid personalized hypertension treatment, especially with respect to hormonal changes, we investigate the extent to which an existing mathematical model of the Renin-Angiotensin System (RAS) can reproduce experimentally observed, hormone level-dependent variations in blood pressure. Since aging itself is one of the main drivers of hypertension, we aim to shed further light on how hormone-independent aging factors and hormonal changes interact in their impact on blood pressure.

First, we identified sex-specific components in an existing Differential Algebraic Equation model to elucidate sensitivity to changes in E2 and Progesterone (P4). Based on the findings, we included hormone-specific coefficients to model components of the RAS, aldosterone, and the mineralocorticoid receptor. Validation against random coefficients confirmed the specificity of the outputs to biologically structured hormonal inputs, reinforcing the mechanistic relevance of the extension. We additionally include progressive deterioration in physiological functions with age, such as baroreceptor activity, glomerular filtration rate and tubuloglomerular feedback signal mediated by decreasing macula densa signaling, as well as increasing cardiac remodeling, arterial resistance, and rarefaction.

Model simulations show a decrease in Mean Arterial Pressure (MAP) of 0.5 mmHg in the follicular phase and 2 mmHg in the luteal phase, based on coefficients derived from experimental studies. These changes, while modest, align with observed trends in menstrual cycle-dependent blood pressure variations and underscore the sensitivity of the RAS to hormonal fluctuations.

The age-related extension leads to a non-linear increase in MAP from 87 mmHg to 107 mmHg over the span of 60 years (covering the ages 20 to 80), consistent with epidemiological data on age-related hypertension.

To our knowledge, this is the first study to incorporate both E2 and P4 impacts on blood pressure regulation with sufficient detail to distinguish the effects of menstrual cycle phases. While the model captures key trends and aligns with qualitative observations from previous studies, it represents a simplified system. Future refinements could include additional blood pressure-regulating mechanisms, further hormonal feedback loops, and the incorporation of menopause-related changes to further enhance its physiological relevance.

Keywords: women’s health, sex differences, blood pressure, hypertension

O10

Strategies for the use of Universal Differential Equations to advance Personalised Medicine.

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Oral presentation

Current medical guidelines often follow a one-size-fits-all approach. While this approach works well for the majority of patients, we consistently see subgroups who experience little to no benefit, with valuable intervention time being lost before the correct treatment can be identified. The identification of patient subgroups and the use of models to predict personalised treatment strategies in the field of oncology have greatly improved the long-term prognosis for people with cancer, demonstrating the potential of computational approaches to advance personalised medicine. However, the machine learning approaches that have proven successful in precision oncology require very large volumes of data to train, which has greatly hampered their application to tackle other diseases. Hybrid modelling approaches, such as physics-informed neural networks and universal differential equations (UDEs), integrate existing physiological knowledge into machine learning models and can be trained with fewer learning examples than comparable machine learning models. However, again their application to biological disciplines has been slowed due to sparse, noisy data sets with small sample sizes and large heterogeneity. We present a conditional approach to training UDEs, where person-specific conditioning parameters are introduced as input to the neural network, the network’s weights and biases can then be trained using

data for the whole population. We applied our cUDE approach to learn a representation for the rate of c-peptide secretion using oral glucose tolerance test data in 118 individuals with varying glucose tolerance status. The model is trained using data for 83 individuals and validated on the remaining 35. We show that, unlike the traditional UDE approach which was unable to generalise to individuals with Type 2 Diabetes Mellitus (T2DM), the cUDE model is capable of describing the diverse patterns of c-peptide production in people with normal glucose tolerance, impaired glucose tolerance and T2DM. Moreover, we also demonstrate that the trained conditional parameter captures interindividual variation in c-peptide production capacity, with a correlation of -0.805 with the first phase of the hyperglycaemic clamp, the gold standard measure of insulin production. In addition to the conditional training, we also introduce a form of physiology-informed regularisation, incorporating additional biological knowledge into the error function during training to penalise undesirable behaviour such as the prediction of negative metabolite concentrations or ensuring all of the glucose from a meal appears within two hours. We show that the incorporation of this physiological information facilitates the recovery of a more biologically plausible model of glucose appearance during a meal even with sparse measurements (every 30 minutes), with the trained model correctly returning to the fasting plasma glucose level when simulated beyond the training data. In this way, we show that hybrid modelling approaches can not only be successfully trained on noisy and sparse human data with a small sample size (<100 individuals), but can also capture physiology-relevant differences in health that can be used in the future for the provision of personalised treatments.

Keywords: Hybrid modelling, Personalised medicine, Scientific machine learning

Computational models for plant growth, stress, and interactions

Chaired by: Anna Matuszyńska

O11

Investigating the principles of plant growth-defence trade-offs in biotic interactions using metabolic modelling

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Oral presentation

Plants enter a defensive state in response to environmental stresses and pathogens, rerouting many resources from their primary growth objective and performing well below their maximum potential. Understanding such growth-defence trade-offs can help us develop improved crop varieties with increased stress tolerance, yield and quality. As potato is among the most important food crops and a model tuber crop species, it is of interest to establish it also as a model system for studying growth-defence trade-offs. To investigate growth-defence trade-offs in the context of metabolism, we developed a compartmentalised genome-scale metabolic model of potato metabolism, Potato-GEM (10.1073/pnas.2502160122). It contains information on the stoichiometry of over 7,000 biochemical reactions, connecting them to the genes encoding the enzymes that catalyse them. We also curated and expanded the Potato-GEM secondary metabolism, capturing its full extent according to the MetaCyc database to produce over 180 distinct secondary metabolites. The potato leaf biomass was quantified using in-house and published experimental data. We employed the model to explore growth-defence trade-offs using transcriptomics data of biotic stress responses to the pathogens Potato virus Y and pest Colorado potato beetle. Condition-specific models recapitulated experimentally observed decreases in relative growth rates under treatment as well as changes in metabolite levels between treatments, enabling us to pinpoint the metabolic rewiring underlying growth-defence trade-offs. We thus demonstrate how the curated model can be used to investigate multi-reaction trade-offs across primary and secondary metabolism by inte-

grating omics data, providing the basis for a metabolic perspective on stress-induced trade-offs typical across many plant species.

Keywords: system biology, potato metabolism, constraint-based modeling, growth-defence trade-offs

O12

Inference of growth and division kinetics in a population balance model of *Chlamydomonas reinhardtii* with Gaussian process regression

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Oral presentation

Population balance models are an established way to simulate the dynamics of a heterogeneous cell population, combining cell growth dynamics and division kinetics in a mathematical model that describes the distribution of cell sizes or other variables over time. They are a useful tool to study the impact of growth and division mechanisms on the heterogeneity of cell sizes within a growing cell population.

Here, we present a population balance model for the model green algae *Chlamydomonas reinhardtii*, which can not only undergo binary division, but also higher order divisions such that the number of daughter cells is a higher power of 2. Experimental data from *Chlamydomonas reinhardtii* grown in photobioreactors under continuous light is used to parametrize the model. Specifically, we determine the growth dynamics and cell size distributions over time from dry mass measurements and flow cytometry, where absolute cell sizes are calibrated from reference beads in combination with a light scattering model to account for the different refractive index between the cells and the beads.

In the population balance model, the growth kinetics and division mechanism are represented by functions of the cell size, which are inferred in a non-parametric way from the measurement data with Gaussian process regression. To this end, suitable reference functions for the regression are defined from the population balance model by considering the measured cell size distribution as steady state. The Gaussian process hyperparameters are then estimated with a maximum likelihood approach.

We show that the estimation procedure is able to robustly parametrize the population balance model. Comparing different division mechanisms, we find that in the process studied here, the cells are mostly undergoing binary division. While this is in contrast to other studies, where quaternary division was found to be more prominent, this difference can possibly be attributed to the use of a different strain or different environmental conditions, specifically a continuous light supply vs. a diurnal light supply. Overall, our study establishes a versatile, data-based approach for mechanistic modelling of cell population dynamics and environment- or strain-dependent variations of division kinetics.

Keywords: Hybrid modelling, Population balance models, Gaussian process regression, Green algae

O13

A metabolic model of the leaf-associated bacterium *Paraburkholderia dioscrae* links the ethylene precursor ACC to core carbon pathways

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Oral presentation

Paraburkholderia dioscrae MSB3 is a newly discovered species with potential agricultural impact, isolated from leaf acumens of the ‘air potato yam’ *Dioscorea bulbifera*. *P. dioscrae*’s genome encodes a relevant combination of features mediating beneficial plant-associated lifestyle and it exhibits significant growth promotion when applied to agriculturally important plants such as tomato. Here we constructed iPR1691, the first genome-scale metabolic model for *P. dioscrae* MSB3, which includes 1687 reactions, 1487 metabolites, and 1691 genes. From an available annotation of MSB3’s genome, a draft model was constructed using an automated approach followed by automatic gap-filling on

KBASE, and was manually curated using constraint-based modeling. *P. dioscarea* MSB3 can grow on 1-aminocyclopropane-1-carboxylic acid (ACC), an ethylene precursor in plants, as a carbon and nitrogen source. As ethylene is a potent growth regulator, associated with fruit ripening, growth arrest, and senescence, ACC consumption has been shown to be a key mechanism in growth promoting bacteria. Based on the reactions and genes present in the model, and on various pathways available on MetaCyc, a pathway for ACC usage in *P. dioscarea* was constructed. Flux Balance Analysis (FBA) was successfully performed to test the growth of *P. dioscarea* on different substrates like glucose, succinate, and ACC, and diverse conditions of carbon, oxygen, and nitrogen availability were simulated. The model was evaluated through Metabolic Model test (MEMOTE), getting a score of 89%. Metabolic models are great tools to gain deeper knowledge and understanding on the metabolism of different organisms. This model provides a representation of the growth of MSB3 on ACC which later could be used to join this model to one of a plant and thus simulate the plant-bacteria interactions. Such a model will allow to further study the plant growth-promoting effects of *P. dioscarea* MSB3.

Keywords: Paraburkholderia dioscarea MSB3, ACC, genome-scale metabolic modelling, Flux Balance Analysis

O14

A systems-level framework for mapping plant heat-stress memory into dynamic regulatory state-space

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Oral presentation

In plant biology, stress memory is a well-known phenomenon in which a previous stress exposure modifies the response to a subsequent stress event. Although there are significant research studies that describe stress memory in plants using experiments and static differential-expression analyses, we still lack models to quantitatively compare stress memory dynamics across datasets and time scales. To address this gap, we are developing a theoretical, computational framework that aims to predict and classify a particular memory pattern in plants exposed to heat stress. We are using previously published, publicly available datasets for Arabidopsis, that include transcriptomic, epigenomic, metabolomic, and physiological measurements. The current framework uses normalized transcript abundance trajectories as input to capture temporal expression dynamics under heat stress. Transcriptomic data from published heat-stress studies were processed and normalized to generate comparable gene expression profiles across recovery timepoints. Differentially expressed genes and temporal expression patterns were then extracted and used as input for the framework to study transcriptional memory dynamics related to heat stress. The framework uses ordinary differential equations (ODEs) to represent transcript activation and decay dynamics over time. This approach allows the detection of dynamic memory states that cannot be resolved using conventional pairwise differential-expression analyses alone. The framework classifies transcript trajectories into transient, intermediate, sustained, and persistent memory states based on temporal stability, decay coefficients, and recovery behavior after heat stress. As proof of concept, we reconstructed theoretical transcript persistence trajectories from published heat-stress datasets and generated dynamic state representations describing different forms of transcriptional memory during post-stress recovery. The conceptual figures produced by the framework illustrate how distinct persistence states emerge from differences in transcript activation and decay dynamics. Our preliminary analysis suggested that heat-stress memory can be described as different transcript behaviors over time rather than only memory versus no memory. Based on activation and decay patterns, we generated theoretical transient, intermediate, and sustained transcript trajectories from published heat-stress recovery datasets and observed that different experiments can show similar persistence behaviors during recovery after stress.

Keywords: Heat Stress, ODE modeling, Stress Memory, Systems Biology, Transcriptomics

Poster session 1

P1

Predicting hepatotoxic metabolites in drug metabolism

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Poster presentation

Drug-induced liver injury (DILI) is one of the leading causes for the termination of drug development. A major contributor to hepatotoxicity is the metabolism of drugs into reactive or otherwise harmful intermediates. Early identification of potentially hepatotoxic compounds therefore plays a critical role in reducing the risk of DILI.

Drug metabolism primarily occurs in the liver, and is largely mediated by cytochrome P450 enzymes. The metabolic reactions can be split into phase I and phase II metabolism. Phase I metabolism introduces or exposes functional groups via oxidation, reduction and hydrolysis. Metabolites that remain insufficiently polar for excretion subsequently undergo phase II metabolism, in which conjugation reactions attach polar moieties to increase water solubility and allow for excretion.

In this work we present a novel computational pipeline for predicting toxic metabolites resulting from phase I and phase II drug metabolism. Candidate drugs are entered into the pipeline, and undergo reactions that are defined using RDKit to generate possible metabolites. These metabolites are then screened for potential hepatotoxic effects using a machine learning-based enzyme-substrate prediction tool [1]. The pipeline successfully identifies known toxic metabolites across a range of well-characterised drugs, demonstrating its potential as an early-stage tool for hepatotoxicity assessment in drug discovery.

[1] Kroll, Alexander, et al. "A general model to predict small molecule substrates of enzymes based on machine and deep learning." *Nature communications* 14.1 (2023): 2787.

Keywords: drug metabolism, systems medicine, hepatotoxicity

P2

Oxygen-dependent restructuring of circadian sterol biosynthesis in HepG2 cells revealed by generalised CosinorPy modelling of LC/MS-MS time-series data

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Poster presentation

Cholesterol biosynthesis is a tightly regulated metabolic network subject to both circadian regulation and oxygen availability. However, how oxygen concentration modulates the circadian behaviour of the sterol pathway remains poorly understood. Here we present a time-resolved, systems-level analysis of the post-squalene sterol pathway in HepG2 human hepatocellular carcinoma cells cultured under three oxygen conditions: hypoxia (1% O₂), physioxia (5% O₂), and normoxia (21% O₂). Cells were cultivated in triplicate for 51 hours, with samples collected every 3 hours, yielding 18 time points per condition. Twelve post-squalene sterol intermediates were quantified using liquid chromatography-tandem mass spectrometry (LC-MS/MS) and normalized to total protein content by BCA assay. Rhythmicity analysis was performed using CosinorPy, a Python framework implementing a generalized cosinor model. This approach estimates both the values and statistical significance of key rhythmicity parameters including amplitude, acrophase, and a time-dependent amplification term within a single statistical model, enabling detection of both stationary and amplitude-modulated oscillations, extending beyond the capabilities of classical cosinor analysis. Most sterol intermediates exhibited significant circadian rhythmicity, demonstrating that the post-squalene sterol pathway functions as a coordinated oscillatory metabolic system. However, oxygen concentration markedly reshaped this oscillatory organization.

Cholesterol and dihydro-FF-MAS were rhythmic at 1% and 5% O₂, but lost detectable oscillation under normoxia ($q = 1.0$). In contrast, proximal intermediates including lanosterol, FF-MAS, and T-MAS maintained robust rhythmicity across all oxygen conditions. Downstream intermediates zymosterol, 7-dehydrodesmosterol, and desmosterol remained rhythmic, but lost the stronger oscillations seen at lower oxygen concentrations. Notably, decreasing oxygen concentration increased the amplitudes of FF-MAS, T-MAS, 24,25-dihydrolanosterol, and dihydro-FF-MAS, suggesting reinforcement of oscillatory dynamics in the proximal pathway under low oxygen conditions. Oscillation amplitudes gradually decreased over the 51-hour period, likely due to progressive desynchronization of cells in the absence of external timing cues. Acrophase analysis also revealed phase shifts between oxygen conditions, indicating that oxygen influences not only sterol metabolism, but also the timing of circadian oscillations across the pathway. These results demonstrate that the post-squalene sterol network operates as an oxygen-sensitive oscillatory system, with physiological and hypoxic oxygen levels preserving rhythmic structure that is disrupted at atmospheric oxygen. Additionally, this work illustrates the power of generalized cosinor modelling for characterizing complex oscillatory dynamics in metabolic time-series and how systems-level temporal profiling can reveal hidden regulatory layers in metabolic networks.

Keywords: Circadian rhythms, Generalised cosinor model, Hypoxia, Post-squalene cholesterol biosynthesis, Time-series metabolomics

P3

Investigating the Reversibility of Rubisco's Catalytic Mechanism and Its Implications for Carbon Fixation Models

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Poster presentation

Ribulose biphosphate carboxylase/oxygenase (Rubisco) is the primary enzyme responsible for photosynthetic carbon fixation through the Calvin Benson cycle. While claimed to be the most abundant protein on Earth, important aspects of Rubisco's catalytic mechanism remain unsolved. Rubisco catalyzes both the carboxylation and oxygenation of ribulose-1,5-bisphosphate, producing 3-phosphoglycerate (3PG) during carboxylation and 2-phosphoglycolate (2PG) during oxygenation. Typically, the Rubisco mechanism is modelled as largely irreversible under physiological conditions. This assumption shapes how isotope fractionation during carbon fixation is interpreted.

In this study, we develop a mechanistic framework that integrates Michaelis-Menten kinetics with constraints imposed by the Haldane relationship to evaluate the potential for reversibility within the Rubisco reaction. The model predicts that under specific conditions, low but non-negligible reverse fluxes can occur. These backward reactions would have implications for the interpretation of the carbon isotope effect expressed by Rubisco in modern systems and over Earth history.

To experimentally test this prediction, we perform enzyme assays to complement the modelling approach. The experimental design involves reaction of an excess of 3-phosphoglycerate (3PG), the product of the Calvin cycle, in the presence of active Rubisco under low CO₂ levels and relatively high O₂ levels, as well as reduced pH of approximately 7.5 compared with the physiological pH of approximately 8.5. Under these conditions, the formation of the oxygenation product 2-phosphoglycolate (2PG), would indicate a reverse reaction of steps within the mechanism. The experimental design and quantification of the results will be informed by theoretical calculations and a dynamic model of the Rubisco-catalyzed chain of reactions.

By bridging the gap between theoretical kinetic modelling and experimental biochemistry, this work seeks to improve the isotopic models used to interpret carbon isotope signatures preserved in organic matter and carbonate minerals. Our findings may challenge the traditional view of Rubisco as an irreversible catalyst, providing a more detailed explanation for isotope effects in photosynthetic organisms and opening new possibilities for optimization of carbon fixation pathways in synthetic biology and climate mitigation strategies.

Keywords: Rubisco, Carbon Isotope Fractionation, Enzyme Kinetics

P4

Analysing energy dissipation partitioning in different environmental conditions with the help of a mechanistic model of proton-motive force

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Poster presentation

Plants experience rapid fluctuations in light intensity under natural conditions. These fluctuations can generate excess excitation energy that exceeds the capacity of the photosynthetic electron transport chain, which drives the process of photosynthesis, and may lead to photodamage. To maintain photosynthetic efficiency, plants rely on photoprotective mechanisms that dissipate excess energy and regulate the energy flow on timescales ranging from seconds to hours.

Here, we present a dynamic mechanistic model of C3 photosynthesis in *Arabidopsis thaliana* that integrates photosynthetic electron transport, the Calvin–Benson–Bassham cycle, cyclic electron flow, reactive oxygen species scavenging, and proton-motive force (PMF) dynamics, including explicit representation of membrane potential ($\Delta\Psi$), and its regulation by ion channels. The model reproduces three independent, distinct classes of measurements: carbon assimilation, non-photochemical quenching (NPQ), and electrochromic shift (ECS) dynamics using a single parameter set, demonstrating consistent agreement across multiple physiological observables and mutant conditions.

The explicit description of PMF composition and ion transport enables the analysis of short-term thylakoid responses under rapidly changing light conditions. Simulations in dynamic light environments representative of field conditions reveal how energy dissipation is redistributed between photoprotective pathways and how PMF partitioning helps maintain photosynthetic stability under stress. The model provides a quantitative framework for investigating the role of ion-channel-regulated PMF dynamics in photoprotection and fluctuating-light acclimation.

Keywords: ODE Model, Photosynthesis, Proton-motive force, Photoprotection

P5

Explainable graph neural networks for condition-specific gene expression analysis and link prediction in Arabidopsis

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Poster presentation

An important prerequisite to understanding how a plant functions and responds to the environment is to determine which gene expression patterns are associated with a specific tissue type and external perturbation response. Neural network-based methods can provide subsets of highly informative genes for such predictions using backpropagation-like explainability methods. Here, we propose that integrating prior molecular knowledge related to gene expression within graph neural network architectures can lead to more reliable and insightful models, improving the identification of tissue- and perturbation-related gene sets and enabling the prediction of novel molecular interactions.

We first construct an *Arabidopsis thaliana* tissue- and perturbation-specific gene expression resource from published datasets and metadata. We then develop a pipeline comprising batch effect correction, prediction training, link prediction, and model explanation. To address batch effects we implement and evaluate several approaches, including ComBat, ComBat-Seq, limma, a proportional gene expression method, and a Gaussian Conditional Variational Autoencoder with scArches-style surgery for projecting unseen experimental batches. Next, we used the Comprehensive Knowledge Network as a source of protein-DNA and protein-protein interactions. We develop and train a relational graph neural network,

combining graph convolution and attention mechanisms over heterogeneous interaction types, to jointly classify the underlying tissue types and perturbation groups using gene expression patterns as input, incorporating the prior molecular knowledge as additional network structure. We further extend the model to link prediction within the knowledge graph, enabling the identification of novel candidate molecular interactions.

The analysis of model explainability, by computing class-specific relevance scores per gene, demonstrates that knowledge graph-primed models outperform baseline models by prioritising biologically relevant genes known to be related to specific tissue types and molecular processes, including phytohormone and stress-related responses. Our results thus demonstrate the applicability and reliability of knowledge graph-primed deep learning for identifying condition-specific genes and gene sets, as well as for predicting candidate molecular interactions in plant transcriptomics.

Keywords: networks, deep learning, interactions, gene expression

P6

Potatoes local Ca²⁺ signalling in space and time

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Poster presentation

Plants constantly monitor their environment and assess where and when to respond to stresses ranging from drought and heat to attack by herbivores or pathogenic bacteria. As plants lack specialised immune cells, each cell must independently detect and integrate the full range of stresses via a small number of molecules, such as receptor proteins, Ca²⁺ ions, and reactive oxygen species. Once stress is identified, cells use paracrine signalling to communicate with surrounding cells, instructing them how to reprogramme themselves to form a distinct and effective response to defend the plant as a whole. Ca²⁺ signalling is central to cell-to-cell communication, forming a distinct spatiotemporal pattern that varies according to the type or combination of stresses.

Mechanistic modelling provides a platform for describing complex non-linear biological processes. To understand the basis of cell-to-cell communication, which operates at multiple spatial and temporal scales, we built a mechanistic model of Ca²⁺ signalling in a plant leaf. The model is based on prior knowledge — experimentally confirmed one-on-one interactions between different molecules in the signalling pathway, including Ca²⁺ ions, reactive oxygen species, receptor proteins, and Ca²⁺ channels. To elucidate the complexity of behaviour in the spatiotemporal dimension, the model is spatially constructed in a two-dimensional grid where cells are distributed similarly to those in a leaf, while temporal dynamics are simulated using Tellurium, a versatile Python environment for ODE modelling. Using the mechanistic model, we tested different stress scenarios and their combinations to determine crucial structures of the model that enable plants to respond appropriately.

To experimentally determine the effect of different stress scenarios, we are using a sensor potato plant, *Solanum tuberosum* Desiree cultivar, with the p35S::GCaMP::NOS vector. The transgenic vector encodes a fusion protein, GCaMP, composed of green fluorescent protein, calmodulin, and peptide M13, which is stably expressed and localised in the cytosol. GCaMP dynamically binds cytosolic Ca²⁺ ions, resulting in high fluorescence. We exposed the sensor potato leaf to wounding with or without pathogenic or beneficial bacteria. We used the experimental data to parameterise the mechanistic model and, through comparative analysis, determined crucial changes between different stresses in the mechanistic model.

This approach combined data on Ca²⁺ signalling from both experimental and modelling perspectives and aimed, to some extent, to explain differences between beneficial and pathogenic bacteria after wounding. In the future, the Ca²⁺ signalling model will be combined with other downstream phytohormone models, such as jasmonic and salicylic acid models, to uncover the full scope of spatiotemporal regulation.

Keywords: systems biology, signalling, plants, calcium, plant immune system

P7

Bioelements: A tool to investigate biological phenomena in 2D

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Poster presentation

Biological phenomena span multiple spatial scales, each governed by distinct physical forces that shape the trajectories of living systems. At the molecular scale, stochasticity and macromolecular crowding dominate, while at higher levels of organization, emergent properties and collective behavior become apparent. To investigate dynamics across spatial scales, researchers use simplifications and mathematical models, enabling computational analysis. Various approaches, ranging from complex to simple, exist for simulating the movement of biological particles or their placement on membranes. Here, we present bioelements, a Python package that allows the particle-based simulation of spatial biological phenomena in two dimensions across scales. Bioelements enables researchers to investigate, among others, bacterial growth, tissue organization, and membrane architecture. For this, bioelements includes a simple physical engine that integrates forces between biological entities, thereby enabling realistic interactions. Moreover, various geometric methods are implemented to prevent particle overlaps and to facilitate placement in crowded environments. Bioelements' main principle is modularity, which allows researchers to adapt the tool for their own research purposes. For instance, most parts of the simulation loop can be changed by custom functions. Finally, bioelements aims to provide quick, easy access to advanced simulation techniques, allowing novices and experts alike to test hypotheses and ideas using two-dimensional spatial simulations.

Keywords: spatial modeling, crowded environments, tissue organization, bacterial growth, software

P8

Spatial transcriptomics analysis of complex skeletal muscle architecture

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Poster presentation

Imaging-based spatial transcriptomics platforms such as Xenium (10x Genomics) enable subcellular-resolution spatial gene expression profiling, but existing analytical workflows are primarily designed around conventional single-cell assumptions that are poorly suited to structurally complex tissues. Skeletal muscle presents a particularly challenging computational setting due to its elongated multinucleated myofibres, heterogeneous supporting cell populations, and dense spatial organization, which complicate segmentation, transcript assignment, and downstream spatial analysis.

Here, we present a computational framework specifically adapted for Xenium skeletal muscle datasets that overcomes these limitations through compartment-specific analytical design. Rather than imposing a uniform cell-centric analytical strategy across the entire tissue, the framework combines fibre-resolved analysis of multinucleated myofibres with nuclei-resolved analysis of surrounding mononuclear cell populations, enabling biologically appropriate treatment of structurally distinct tissue compartments. The framework integrates tissue-adapted segmentation, transcript-to-mask assignment, quality control, clustering, annotation, and spatially variable gene (SVG) analysis.

The framework was developed and evaluated using tibialis anterior datasets from a polygenic mouse model (16 mice). To assess analytical performance, we combined experimental validation with systematic benchmarking of downstream computational methods. Fibre-type annotation was evaluated against immunohistochemistry-derived reference labels, while clustering performance and SVG detection approaches were assessed using experimental and synthetic spatial transcriptomics datasets gen-

erated under controlled conditions. This benchmarking strategy enabled evaluation of reproducibility, robustness, and method-dependent variability across key analytical steps.

Our analyses demonstrate substantial variability in downstream results depending on computational method choice, particularly for spatially variable gene detection. These findings highlight the importance of tissue-aware analytical design when applying imaging-based spatial transcriptomics to morphologically complex tissues, where standard single-cell assumptions may not be biologically appropriate.

This work provides a reproducible and modular analytical strategy for skeletal muscle imaging-based spatial transcriptomics while offering practical guidance for method selection in high-resolution spatial transcriptomics analysis. Although developed for skeletal muscle, the underlying analytical principles may be transferable to other structurally complex tissues that challenge conventional spatial transcriptomics workflows.

Keywords: Imaging-based spatial transcriptomics, Skeletal muscle, Complex tissue architecture, Computational framework

P9

Cellular Economics of Exchanged Metabolites Alter Ratios of Microbial Trading Partners in Predictable Manner

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Poster presentation

Most microorganisms exist in interacting consortia, yet the principles behind consortia assembly, including trading partner structure, still require deciphering despite being central to understanding, building, and controlling consortia. This study tests a cellular economy-based hypothesis that proposes consortia engaged in obligate metabolite exchange will assemble at ratios where the metabolic burden associated with the exchanges is predictably shared. The metabolic burden was quantified using ATP equivalents, the quantity of high energy ATP phosphoanhydride bonds that could be produced if the exchanged metabolites were instead retained and catabolized for cellular energy. The hypothesis was tested using *Escherichia coli* cocultures engineered for obligatory exchange of pyruvate and L-arginine. The burden of metabolite exchange was manipulated by changing O₂ availability, which altered the bioavailability of substrate energy, and by deactivating the ATP synthase enzyme, which prevented oxidative phosphorylation. Three synthetic cocultures assembled at predicted strain ratios as a function of the perturbations. The strain ratios represented an equivalent metabolic burden between the trading partners even though the exchanged metabolites varied substantially in flux magnitude (300+ fold), molecular weight (174 vs. 88 g mole⁻¹), enzyme requirements (8 specialized enzymes vs. none), and biological energy density (27.5 vs. 9 ATP molecule⁻¹). The strain ratios could be rationally altered up to 20-fold using O₂ availability and cellular phenotype. The metabolic burden theory was applied to seven additional published cocultures and found to accurately predict trading partner ratios. Quantifying exchanged metabolites on an ATP equivalents basis provides a theory for interpreting natural consortia and a toolbox for controlling bioprocess consortia.

Keywords: synthetic ecology, cellular economics, microbial consortia, consortia assembly, systems biology

P10

Towards a Reproducible Thermodynamic Model of E. coli Gene Regulatory Network for the In-Silico Design of Unconventional Computing Platforms

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Poster presentation

Gene regulatory networks (GRNs) have been proposed as potential substrates for unconventional computing, enabling biological systems to process temporal information and compute desired outcomes.

Previous work has suggested that the GRN of *E. coli* may have liquid state machine properties. However, reproducibility of such models is severely limited by unavailable datasets and underspecified implementation details.

Herein, we present a reconstruction and extension of thermodynamic model of the *E. coli* GRN, grounded in the transcriptional regulation formalism of Bintu et al. (2005)[1] and the framework of Jones et al. (2007)[2]. The original publications were augmented with additional recent datasets to implement a complete pipeline for generating systems of ordinary differential equations (ODEs) describing mRNA and protein concentrations over time in the proposed network. The framework systematically incorporates transcription factor interactions with cognate operons, including activation, repression, and probabilistic pairwise cooperativity.

The proposed work represents a reproducible pipeline for reconstruction of GRN models with predefined characteristics from a file containing a list of interactions between transcription factors and operons. Our implementation thus provides a flexible platform for the analysis of computational capabilities and limitations of GRNs for use as unconventional computing platforms.

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Keywords: reservoir computing, GRN, modeling

P11

A multi-meta-omics study of microbial metabolic potential and its manifestations in marine microbial communities

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Poster presentation

Division of metabolic labor is a major trait of natural microbial communities, which perhaps explains why they have evolved to become efficient biochemical powerhouses, and why human-made synthetic biology designs frequently struggle with their tasks. Can we codify and leverage the patterns of how natural microbial communities compartmentalize mutually incompatible metabolic pathways and/or metabolite cross-feeding for rational design of microbial cell factories? We would like to tackle this question by establishing a multi-meta-omics-informed modeling framework, built around reanalyzing the sequencing data from 44 samples from the TARA Oceans expedition, for which coupled shotgun metagenomes and metatranscriptomes have been acquired. To quantify the metabolic potential in marine microbial communities, we reconstructed genome-scale metabolic models (GEMs) for both the entire metagenome assemblies ("bag-of-genes" approach, $n=44$), as well as all metagenome-assembled genomes (MAGs; $n=1,907$). We next mapped the metatranscriptomic reads onto the genes present in GEMs to identify the expressed parts of the metabolic potential using statistical inference (e.g. inter- and intrasample correlation and covariance). We will bridge our observations towards mechanistic insights, introducing thermodynamic driving force and enzyme cost calculations based on reaction stoichiometry, stored in GEMs. By learning from the design rules and "economics" of natural microbial communities - including these 44 marine communities - we hope to contribute design tools and frameworks to tackle the grand challenge of synthetic biology: rational, bottom-up design of synthetic metabolic networks.

Keywords: genome-scale metabolic modeling, meta-omics, microbial communities

Metabolic modelling and multi-omics approaches in cancer research

Chaired by: Miha Moškon

O15

Constraints-based metabolic modelling identifies ME2–ME3 synthetic lethality in temozolomide-resistant glioblastoma

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Oral presentation

Glioblastoma multiforme (GBM) remains uniformly fatal due to treatment-resistant subpopulations whose metabolic vulnerabilities are incompletely mapped. Synthetic lethality, where simultaneous loss of two genes is lethal while loss of either alone is tolerated, offers a route to selective targeting, but the experimental space of gene-pair combinations across multiple resistance states is too large to map exhaustively in cell-based screens. Here we use constraints-based Genome-Scale Metabolic Models (GSMMs) to predict synthetic lethal (SL) pairs in three GBM states with distinct metabolic architectures: temozolomide-sensitive LN229, parental U87MG, and FACS-isolated TMZ-resistant neurospheres (NSP) derived from U87MG. Cell-line-specific GSMMs were constructed by constraining a curated central-metabolism reconstruction with measured uptake and secretion fluxes, and validated against experimentally measured growth rates. Exhaustive in silico double-gene deletion analysis evaluated all 242,064 unique gene-pair combinations per model. Of these, malic enzyme 2 (ME2) and malic enzyme 3 (ME3), both mitochondrial isoforms catalysing oxidative decarboxylation of malate to pyruvate, emerged as the single SL pair unique to NSP. Monte Carlo Artificial Centering Hit-and-Run sampling (50,000 points per genotype) showed that NSP cells uniquely lack the cytosolic compensatory flux flexibility available to U87MG when the mitochondrial malic enzyme node is perturbed, providing a mechanistic basis for the prediction. siRNA-based validation across the three cell lines confirmed the prediction: combined ME2 and ME3 silencing produced selective cytotoxicity in NSP at IC50 values 5-fold lower than LN229 (3.86 nM vs 19.03 nM; $p < 0.05$). Silencing of the cytosolic ME1 isoform produced the opposite sensitivity pattern (NSP 2.7-fold more resistant than LN229), confirming a mitochondrial-specific dependency rather than a general malic enzyme requirement. NSP cells were not preferentially sensitive across a panel of five mechanistically diverse non-target inhibitors, indicating that the synthetic lethal vulnerability is mechanism-specific rather than reflective of a broadly drug-susceptible phenotype. The mitochondrial malic enzyme axis represents a selective vulnerability of resistant glioblastoma neurospheres. More generally, synthetic lethal interactions in our analysis emerge at metabolic nodes where cell-line-specific architectural redundancy is absent. The work demonstrates the value of cell-line-calibrated constraints-based modelling for systematic SL discovery in cancer subpopulations.

Keywords: genome-scale metabolic modelling, synthetic lethality, glioblastoma, malic enzymes, flux sampling

O16

Analysing tumour heterogeneity using scRNA-seq data and genome-scale metabolic models

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Oral presentation

Malignant tumours are caused by a series of complex genetic mutations. As tumours develop, they become more heterogeneous. Tumour tissue is therefore composed of a diverse collection of cell types that create a continuously evolving tumour microenvironment. This heterogeneity poses a significant challenge for both cancer research and treatment [1]. Conventional sequencing methods, such as bulk

RNA sequencing, pool large numbers of cells, masking rare clones and limiting the ability to track mutations during tumour progression. In contrast, scRNA-seq enables transcriptome analysis at the level of individual cells, allowing precise identification of distinct cell populations within tumours. This provides a high-resolution view of tumour heterogeneity and enables detection of rare cell populations that may drive tumour progression and therapy resistance. Tumour metabolism is greatly altered during tumour progression [2], which was the focus of this work. Context-specific genome-scale metabolic models (GEMs), built using HumanGEM [3] as a reference and tumour cell scRNA-seq data, were used to explore and analyse metabolic pathways in silico by modelling active biochemical reactions in a context. Two separate scRNA-seq datasets were used to build our models. The first contained healthy pancreas tissue as well as tumour samples with pancreatic ductal adenocarcinoma [4], while the second contained only cancerous prostate tissues [5]. Both datasets were obtained from a publicly available database and processed using Seurat R package. Cells were clustered and annotated by cell types, and pooled clusters were used to generate the GEMs via the ftINIT algorithm. Biological consistency between the actual data and generated models was evaluated using distance metrics, including Euclidean and Pearson distances. These were compared between normal and tumour cells both before and after generating GEMs to guide the reconstruction of biologically relevant context-specific GEMs. The obtained models allow us to identify reactions that differ between cell types within tumour tissue, providing deeper insight into tumour heterogeneity. Tumour tissue exhibits substantial heterogeneity not only within individual tumours but also among tumours of the same type in different patients, a pattern that can also be observed from model-based analyses. Furthermore, the study highlights the potential of scRNA-seq-based GEMs to advance our understanding of tumour metabolism and heterogeneity. By capturing metabolic diversity at the single-cell level, they provide a more detailed view of intratumoral variation, potentially facilitating the discovery of novel therapeutic targets. References [1] F. Wei et al., *Cell. Mol. Life Sci.* 78, 173–193 (2021). [2] W. Zou, D. R. Green, *Cell Metabolism*. 35, 1101–1113 (2023). [3] J. L. Robinson et al., *Science Signaling*. 13, eaaz1482 (2020). [4] E. S. Carpenter et al., *Cancer Discov.* 13, 1324–1345 (2023). [5] X. Ma et al., *Mol Cancer*. 19, 147 (2020).

Keywords: genome-scale metabolic modelling, tumour heterogeneity, scRNA-seq data

O17

Integrated Multi-Omics and Flux Analysis Reveal Cell-State-Dependent Metabolic Responses to Dichloroacetate in Melanoma

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Oral presentation

Introduction: Dichloroacetate (DCA) has been proposed to suppress glycolysis in cancer by inhibiting pyruvate dehydrogenase kinases (PDKs) and promoting mitochondrial oxidation of glucose-derived pyruvate. However, the metabolic determinants that govern cellular responsiveness to DCA remain poorly defined. Here, we investigated how baseline metabolic states shape the response to DCA in melanoma cells by applying time-course [U13C]-labeling experiments and Isotopomer Network Compartmental Analysis (INCA) modeling to quantify glycolytic, pentose phosphate pathway and tricarboxylic acid (TCA) cycle fluxes. **Methods:** We combined extracellular flux measurements, quantitative targeted proteomics, enzyme activity profiling, and ¹³C metabolic flux analysis to compare basal metabolism and DCA response in metabolically distinct melanoma cell lines, including the highly glycolytic A375 and the more oxidative SK-MEL-2 cell lines. Dynamic flux modeling was performed using INCA to quantitatively infer glycolytic and pentose phosphate pathway fluxes from time-resolved isotope labeling data. An isotopic steady-state model was used to infer TCA cycle flux. **Results:** The response to DCA differed between melanoma cell lines. Baseline profiling revealed that A375 cells exhibited high glucose uptake and near-stoichiometric conversion of glucose to lactate, whereas SK-MEL-2 cells directed a larger fraction of glucose-derived carbon toward mitochondrial oxidation. In A375 cells,

DCA induced pronounced metabolic rewiring characterized by reduced lactate production, increased pyruvate entry into mitochondria, and a relative shift in glucose-6-phosphate utilization toward the pentose phosphate pathway. In contrast, SK-MEL-2 cells showed slightly increased lactate production without a clear increase in mitochondrial flux. Proteomics data reflect the observed flux differences. Conclusion and outlook The effects of DCA on melanoma cells depend on the baseline carbon flux distribution, particularly the balance between glycolytic, pentose phosphate pathway, and TCA cycle fluxes. We are currently developing an ODE model to predict flux distributions from proteomics data. This may ultimately be applied clinically to stratify tumours for DCA treatment.

Keywords: Dichloroacetate, Melanoma metabolism, ^{13}C metabolic flux analysis, Dynamic INCA modeling, Pentose phosphate pathway

O18

Transcriptome-driven constraint-based modelling reveals metabolic targets for ovarian cancer

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Oral presentation

Constraint-based modelling (CBM) is a powerful computational approach that reconstructs cellular metabolism by integrating ‘omics data with genome-scale metabolic models (GEMs), enabling in silico hypothesis generation and genetic engineering studies. Advances in high-throughput ‘omics technologies and the complete mapping of the human genome have expanded the application of CBM to human systems. Given that altered metabolism is a hallmark of cancer, this disease represents an ideal context for developing and applying CBM workflows. Despite the presence of well-characterised metabolic signatures and vulnerabilities in ovarian cancer, this tumour type remains under-explored within the CBM field. Meanwhile, the limited efficacy of current therapies and the frequent emergence of chemoresistance underscore the need for novel, mechanism-based approaches to therapeutic discovery. In this study, we constructed ovarian cancer-specific metabolic models using an ‘omics integration algorithm that incorporates transcriptomic data in a way that is directed by experimental proliferation measurements. Simulations identified multiple candidate molecules predicted to influence cancer cell proliferation. Among these, triosephosphate isomerase 1 (TPI1) was selected for experimental validation based on qualitative prioritisation criteria. Notably, model predictions were supported by RNA sequencing and colony-formation assays, implicating TPI1 in ovarian cancer cell survival. Our results provide novel insights into the metabolic dependencies of ovarian cancer and demonstrate an omics-integrated CBM workflow that may be broadly applicable for uncovering therapeutic vulnerabilities in other malignancies.

Keywords: Constraint-based modelling, Ovarian cancer, Triosephosphate isomerase 1, Cancer metabolism, RNAseq

Refining and engineering the predictive blueprint of microbial cells

Chaired by: Anže Županič

O19

Cell Geometry and Membrane Protein Crowding Constrain Escherichia coli Growth Rate, Overflow Metabolism, Respiration, and Maintenance Energy.

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Oral presentation

The rules of prokaryotic cell design remain elusive. Here, a theory is presented for interpreting growth rate, overflow metabolism, respiration efficiency, and maintenance energy flux based on cell dimensions, membrane protein crowding, and metabolism. The theory employs biophysical properties and systems analysis to successfully interpret phenotypes of *Escherichia coli* K-12 strains MG1655 and NCM3722. These strains are genetically similar but differ in surface area-to-volume (SA:V) ratios (~30%), growth rate on glucose (~40%), and overflow-inducing growth rates (~80%). Six predictions were tested and validated using experimental phenomics, proteomics, and mutant data. Analyses did not require assumptions regarding cytosolic macromolecular crowding highlighting the distinct properties of the theory. Cell geometry and membrane protein crowding are significant biophysical constraints of cell biology.

Keywords: cell geometry, surface area : volume, cell biology, rules of life, systems biology

O20

Thermodynamics of Microbial Growth under nutrient limitation

Oliver Ebenhöh

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Oral presentation

Microbial growth is often described as a thermodynamic energy converter, in which the catabolic breakdown of nutrients yields free energy which is partly used to drive the anabolic processes that assemble nutrients into new biomass. The combined effect of anabolism and catabolism can be described by a so-called "macrochemical" equation, which summarizes the chemical conversion of nutrients into catabolic waste products, biomass, and possibly other side products. Because such a description of microbial growth completely ignores the details of intracellular metabolism, it is often termed a "black box" model of microbial metabolism. A diametrically different approach to describe metabolism is by genome-scale metabolic network models. Such models are derived from annotated genome sequences and ideally comprise all known biochemical reactions that can occur inside an organism.

We here investigate how these two concepts can be combined to study the thermodynamics of microbial metabolism. We illustrate how experimentally determined macrochemical equations can be systematically separated into a catabolic and an anabolic part. We then characterize these separate chemical equations by their thermodynamic properties and derive the generalized thermodynamic forces and flows that correspond to the affinities of catabolism and anabolism, and the corresponding catabolic and anabolic rates. With these data we challenge the common view that microbial energy conversion can be described by a linear energy converter model.

We systematically analyse chemostat growth data for a variety of microbes under carbon and non-carbon limited conditions to calculate the thermodynamic driving forces. We observe that the catabolic driving force, normalised to carbon mole new biomass formed, is consistently higher for non-carbon limited conditions over carbon limitation. Our observations hold for yeasts as well as bacteria and extend over a variety of limitations (nitrogen, sulfur, potassium, and phosphate). This systematic increase of catabolic driving force per biomass formed under anabolic limitations indicates a novel thermodynamic principle of microbial growth. Understanding this increase systematically will be important for biotechnological applications. Often, anabolic limitations are applied to induce the production of valuable side products, but as a consequence the heat generation drastically increases. A quantitative understanding of the thermodynamic gradients, and thus also heat production, under anabolic limitations will be critical to optimise bioreactor-based biotechnological production processes.

Keywords: microbial growth, thermodynamics, metabolism

Are Computational Predictions of Essential Genes as precise as Experiments?

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Oral presentation

A comparative analysis of gene essentiality predictions by TraDIS (Transposon Directed Insertion Site Sequencing) experiments, with individual gene knockouts in the Genome Scale Metabolic Models (GSMs) showed 90% agreement. These results were also compared with experiments performed to predict genome-wide essentiality in a previous study [1] and the three-way comparison showed similar agreement. These methods were first tested on a lab strain of E.coli (MG1655) and then applied to the clinical strain. In order to identify shifts in metabolic responses of resistant bacteria to antibiotic treatment, experimental data was integrated into analysis of GSM of the clinical strain, with the aim of identifying novel antimicrobial targets.

The GSMs of the two strains of E.coli were constructed and analysed using established techniques. TraDIS experiments were performed by the collaborators and details were published previously [2]. The results from these experiments were compared with in silico gene knockouts in the GSMs. The quantitative impacts of knocking out the genes in the GSMs were calculated using different metrics which will be discussed in detail. These metrics were compared with experimental metrics by contingency table analysis and showed approximately 90% agreement in predicting the gene essentiality. After establishing the concordance of the two methods, computational methods were also applied to the GSM of the clinical strain of E. coli, a veterinary pathogen used in the study by collaborators. The data from TraDIS experiments under antibiotic treatment was integrated into the GSM and metabolic pathways responsible for antibiotic resistance were identified. These pathways were involved in cell wall metabolism and the enzymes involved could be potential targets for novel antibiotics.

Therefore, we conclude that the method developed in this study is highly accurate for preliminary predictions of genes essential for bacterial growth. By analysing GSMs on integration with experimental data, novel antibiotic targets were also identified.

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Keywords: Metabolic Modelling, Systems Biology, Gene Essentiality, Antimicrobial Resistance

Generation of metabolomic-informed models of metabolism in complex microbial communities

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Oral presentation

Genome-scale metabolic networks (GSMNs) gather metabolic reactions whose presence prediction in the species is supported by gene-protein-reaction relationships. These networks are used to predict the metabolic potential of species in given environments using flux-based simulations or reasoning-based models. However, their reconstruction remains challenging and most automatically generated GSMNs are still incomplete, missing important functions related to specialised metabolism (SM). Methods are

needed to comprehensively describe SM and integrate it into GSMNs by combining the analysis of metabolomic data with the exploration of genomic annotations.

In this work, we mined metabolomic data to identify the presence of the characterised compounds in GSMNs, revealing that the vast majority of these were absent from major GSMN-associated databases. This confirms the potential for GSMN quality improvement through integration of experimentally validated metabolomic data, enabling more accurate and comprehensive network reconstructions. Yet, mapping metabolomic data to GSMNs is not trivial, and most mappings requires manual or semi-manual curation, a fastidious and error-prone task. To overcome these challenges, we developed MetaNetMap, a Python package that automatically matches metabolomic annotations onto GSMNs. It improves mapping rates through direct i) mapping taking into account metadata of input files, ii) indirect matching by relying on conversion data tables built from third-party knowledge bases, and iii) partial matching techniques. Applications to published datasets highlighted that up to 40% of metabolomic compounds could be automatically mapped to GSMNs, with up to 10% additional matches compared to the original studies.

Unmapped metabolomic compounds can result from SM-related gaps in GSMNs. The identification of biosynthetic gene clusters (BGCs) and their translation into metabolic reactions for integration into GSMNs represents a powerful strategy to address this limitation. Using antiSMASH in conjunction with MiBIG allows us to identify potential BGCs, to determine whether they are already known. We conducted a use-case on *Microcystis* strains and their associated microbial communities, highlighting the need to develop an automated method to filter and validate BGCs based on their quality and identification in MiBIG prior to their integration in GSMNs, as false-positive identifications may occur. We then addressed the matter of GSMN integration by structuring and extracting information from BGCs, such as associated metabolic reactions, metabolites and biosynthetic pathway genes, setting up a framework for reproducible and automated connection between BGC identification and GSMNs.

Overall, by automating the integration of metabolomic data and BGC information, we aim to overcome a major obstacle to multi-omic integration, thereby enabling the more efficient and reproducible development of high-quality metabolic models.

Keywords: Systems biology, Microbial ecology, Metabolic modelling, Metabolomics, Heterogenous data

O23

Metabolic modeling of fungal pathogens – Gains and limitations

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Oral presentation

Next to a severe economic impact due to, e.g., azole resistance, fungal pathogenicity poses an increasing threat to human health. One of the key determinants of fungal virulence is flexible metabolic adaptation, which enables fungi to exploit host nutrients, survive environmental stress, and sustain infection. Understanding the underlying metabolic mechanisms is essential for counteracting pathogenic fungi, however, exploring metabolism in all its facets is infeasible by wet-lab experiment alone. Computational analyses of genome-scale metabolic networks are ideally situated to systematically investigate metabolism and propose potential targets for therapeutic antifungal intervention. We developed metabolic models for three members of the WHO fungal pathogen priority list, all of which can cause devastating invasive fungal infections. Using our *Candida albicans* model we identified key bacterial determinants of fungal colonization levels in the human gut. For *Aspergillus fumigatus* we showed the feasibility of reconstructing strain-level resolved fungal metabolic models and revealed growth dependencies on the lung microbiome. Finally, reconstructing a genome-scale metabolic model of the Mucorales species *Lichtheimia corymbifera* allowed us to propose how the fungus may scavenge host-derived lipids to fortify its own cell membrane. Despite the vast use of growth and OMICs data for reconstruction and

analysis purposes, a number of complications exist, including limited annotation information, different fungal phenotypes, and namespace conflicts across different kingdoms of life. Overcoming these will be crucial to improve model quality, availability and prediction accuracy of individual and community model simulations, which in turn will be pivotal to truly contribute to our understanding of fungal pathogenicity and developing strategies to ultimately tackle the threat fungal pathogens pose to the human society.

Keywords: metabolic modeling, fungal pathogenicity, microbiome

O24

The art of phenotype design: unlocking StrainDesign for complex substrate utilization

Maaïke Remeijer, Ingrid Persitz, Vasilis Flouris, Frank Bruggeman

VU Amsterdam, NL

Oral presentation

Microbial metabolism can be genetically engineered to produce chemicals. Recent developments in synthetic biology allow for extensive rewiring of microbial metabolism. Manual design of metabolic networks, i.e., identifying the knock in/out gene set, is insufficient for genetic engineering with a minimal number of genetic interventions. Algorithms such as StrainDesign [1] compute such interventions from a genome-scale stoichiometric model given a phenotype description and a candidate knock in gene set. These algorithms have mostly been applied to growth-coupled production using a single sugar substrate. More sustainable alternatives include mixed-sugar substrates or non-sugar carbon sources. Designing strains for such substrates requires careful mathematical formulation of the to-be-engineered phenotype. In this work, we present two case studies for the application of StrainDesign: carbon capture by net CO₂ consumption and enforced coconsumption of sugars. For the fixation of CO₂ into biomass (as sole carbon source), a second substrate is required that supplies the charged energy carriers. Often such cosubstrates contain carbon and the consumption of this cosubstrate leads to production of CO₂, making the overall design net CO₂-emitting. An alternative is to use a non-carbon containing cosubstrate, but these bring their own problems. Here, we design metabolic networks for *Escherichia coli*, in which at least 99% of the carbon that is consumed as CO₂ ends up in biomass, with a carbon-containing cosubstrate. Lignocellulosic biomass, one of the most abundant carbon and energy sources on earth, consists of a complex mixture of sugars, motivating enforced co-consumption. Previously, *Saccharomyces cerevisiae* strains have been engineered that can only grow if two sugars are present. Here, we design strains for more complex mixtures. We find that to enforce growth on multiple sugars, each sugar must supply a precursor or energy carrier that the others cannot supply. This implies a maximum number of substrates that can be enforced to be consumed simultaneously, equal to the number of energy carriers and precursors. It is likely that the practical design limit is much lower than that. We conclude that the two case studies demonstrate the importance of phenotype formulation in unlocking the power of StrainDesign for non-trivial metabolic objectives, from net CO₂ consumption to enforced co-consumption of complex sugar mixtures. We envision a future in which a database of enzyme-catalyzed reactions makes any reaction a knock-in candidate.

[1] Schneider, P., Bekiaris, P. S., von Kamp, A., & Klamt, S. (2022). StrainDesign: a comprehensive Python package for computational design of metabolic networks. *Bioinformatics*, 38(21), 4981-4983.

Keywords: Genome scale modeling, Metabolic engineering, Minimal cut sets

Theory and dynamics of metabolic modelling (Part 2)

Chaired by: Johann Rohwer

O25

Use of non-autonomous differential equations in modelling metabolic processes

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Oral presentation

In Theoretical Systems Biology, systems of ordinary differential equations are a widely used tool. Most of these equations are autonomous, that is, they do not explicitly depend on time. The rationale for this approach is that many processes such as growth depend on the state variables such as biomass or metabolite concentrations at any given moment. However, in numerous situations, biological processes are driven by external inputs or genetic programs. For example, food intake, oscillating hormone concentrations or the day-night rhythm can affect metabolic processes. Such driven processes have indeed been modelled by non-autonomous ODEs [1-4]. Another application of such ODEs revolves around plant-herbivore interactions. Most plants store chemical defenses that act as toxins against herbivores. The fitness of herbivorous larvae can be strongly affected by these toxins, causing immature death. We developed a model that helps explain the early larval mortality caused by plant toxins [4]. Our use of non-autonomous equations was motivated by the reasoning that larval development is driven by a genetic program that is implemented in time. If the explicit dependence on time is linear, a power function or a sinus function, all equations can be solved analytically. This can be achieved, for example, by the method of integrating factor or by defining a new variable as a linear combination of the dependent variable and time. Approximative solutions can be found by the so-called adiabatic approximation. We show that this gives better results than the quasi-steady-state approximation and derive the following result: When an antagonistic action affects an organism with a rate linearly increasing in time and that organism counters that with a rate proportional to the accumulated amount of that action, it attenuates the accumulated effect but cannot prevent that this total amount increases linearly in time. The method also allows one to demonstrate that an external input by the day-night rhythm leads to a delay in the internal response.

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Keywords: non-autonomous differential equation, plant-herbivore interaction, day-night rhythm, external input, adiabatic approximation

O26

The dynamic world of metabolic cofactors

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Oral presentation

Metabolic cofactors such as FAD, Coenzyme A (CoA) and NAD are usually interconverted between two different states, like oxidized and reduced forms for NAD and FAD and acylated and free form

for CoA. For NAD it is now well known that it is, in addition, to the reversible interconversion in redox-reactions, consumed and degraded to its precursor nicotinamide (Nam). This requires constant resynthesis from Nam or other precursors and leads to cell type specific half-lives ranging from several minutes to a few hours. We furthermore established an important role of mitochondria in the buffering and maintenance of cellular NAD, recently. We now used stable isotope labelling approaches and high-resolution mass spectrometry to investigate the subcellular turnover of NAD and other metabolic cofactors such as CoA and FAD. Surprisingly, we found comparable high turnover for these cofactors and a comparison of the biosynthesis pathways showed striking similarities between the biosynthesis pathways of these cofactors and their subcellular localization. But while many reactions responsible for the consumption of NAD have been identified in the last 20-30 years, little is known about FAD or CoA consuming reactions. We used mathematical modelling approaches to unravel the interconnection of NAD, CoA and FAD biosynthesis, providing interesting insights into the potential role of mitochondria in cofactor biosynthesis and maintenance.

Keywords: metabolic cofactors, stable isotope labelling, NAD, CoA and FAD

O27

From large networks to large dynamic models: the steps and missteps of going big

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Oral presentation

Large-scale, manually curated knowledge networks are invaluable for organizing complex biological data, but transforming these static maps into predictive, executable models remains a major challenge. In this work, we report on our experiences attempting to translate our Plant Stress Signalling (PSS) network—a large, community-extendable resource of molecular interactions—into a dynamic computational model. Our primary objectives were to evaluate the scalability transforming PSS into a simulatable ODE system and to test whether a simulation-driven pipeline could assist in curating or validating the network’s topological connections.

Our translation workflow attempted to bridge the gap between static topology and kinetic modeling through a multi-step parameterization process. We first used structural network analysis to identify and resolve topological gaps within the PSS network. We then assigned specific reaction rate laws to individual interactions, harvested known kinetic parameters from literature, and applied general physical and thermodynamic constraints. To fill the remaining gaps, advanced AI tools were utilized to predict unknown kinetic rates, and the components were integrated into a unified model using the Tellurium framework.

During the simulation phase, the model served as an aggressive quality control mechanism that exposed hidden curation errors in the underlying network, including missing annotations, incomplete reaction components, and numerical instabilities yielding non-physical negative values. However, resolving these issues also revealed deeper structural and mathematical hurdles. We have not solved all of these modeling bottlenecks, and we present this work not as a finalized, definitive solution, but as a candid case study of the practical challenges encountered when scaling static knowledge into dynamic simulations. By sharing our ongoing experiences, we aim to spark a broader community discussion regarding the feasibility of this translation pipeline and whether it represents the right path forward for large-scale network simulation and validation.

Keywords: systems biology, dynamic modeling, network analysis, kinetics, plants

Model Refinement of Partially Specified Boolean Networks Using Phenotype Control

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Oral presentation

Boolean networks (BNs) are a widely used framework for modelling qualitative dynamics in gene regulation and cell signalling. A persistent challenge in BN modelling is incomplete mechanistic knowledge, which prevents full specification of the network's update functions. Partially specified Boolean networks (PSBNs) address this by encoding ensembles of candidate models consistent with available, but incomplete, biological knowledge.

We present a novel computational framework for control-guided model refinement of PSBNs. The approach integrates phenotype control — perturbations that drive a system towards a desired biological state — into an iterative refinement loop. Rather than requiring the system to reach a specific attractor, we assess phenotypic traits of attractors, including a novel extension to oscillatory phenotypes. This extension is biologically motivated: observed phenotypic traits often describe stages within larger oscillations (e.g. cell cycles, circadian rhythms), and qualitative abstraction in BNs can cause continuous steady states to manifest as oscillations in the Boolean domain.

The refinement workflow proceeds as follows: (1) an initial PSBN is constructed from prior knowledge; (2) phenotype control is computed across all interpretations for a set of admissible perturbations; (3) perturbations are ranked by normalised mutual information score (NMIS), quantifying how well each perturbation outcome reveals unknown model features; (4) high-ranking perturbations are tested in vitro or verified analytically; (5) non-compliant interpretations are excluded, and the loop repeats. Computationally, the method relies on a symbolic encoding using binary decision diagrams (BDDs), enabling efficient calculation of robustness and NMIS across large interpretation spaces without explicit enumeration.

We demonstrate the framework on receptor tyrosine kinase (RTK) signalling, specifically the FGFR3–MAPK pathway relevant to skeletal dysplasias and cancer. In an isolated FGFR3–MAPK model (12 variables, 16 interactions), control-guided refinement reduces 888 candidate interpretations to 18, computationally confirming that SHIP2 loss of function leads to down-regulation of ERK activity — consistent with experimental observations. In a larger, extended model embedding FGFR3–MAPK signalling into the integrative Grieco et al. (2013) MAPK network (54 variables, 104 interactions), the framework reduces over 500,000 interpretations to approximately 53,000 and confirms the robust effect of PLCG perturbations on proliferation.

Our results demonstrate that control-guided refinement can generate actionable hypotheses for experiment design, narrow model uncertainty, and confirm biologically relevant insights — offering a principled, scalable approach to iterative model identification in systems biology.

Keywords: Boolean networks, model refinement, phenotype control, MAPK signalling, fibroblast growth factor receptor

Poster session 2

P12

NAViFluX: A Visualization-Centric Workbench for Interactive Analysis, Refinement, and Design of Genome-Scale Metabolic Networks

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Poster presentation

Genome-scale metabolic networks (GSMNs) are foundational to systems biology, enabling quantitative modelling of cellular metabolism in organisms ranging from microbes to human cell lines. Despite their

power, routine use of GSMNs remains bottlenecked by fragmented ecosystems: flux analysis, model curation, and visualization are typically siloed across incompatible tools, each demanding considerable bioinformatics expertise. This limits the ability of experimental biologists to engage in iterative, hypothesis-driven metabolic reasoning. We present NAViFluX, a visualization-centric workbench that unifies GSMN exploration, refinement, construction, and analysis within a single interactive environment requiring no programming expertise. NAViFluX offers four distinguishing capabilities: (i) native generation of pathway and subsystem maps directly from GSMN annotations using intuitive network layouts, bridging the gap between raw model files and interpretable pathway maps; (ii) interactive reaction-level editing including constraint modification, reaction addition or deletion, and gap-filling using curated BiGG and KEGG databases; (iii) subsystem grouping into higher-order pathways to support pathway-level biological reasoning; and (iv) integrated analyses including flux balance analysis (FBA), gene knockout and synthetic lethality simulations, network topology metrics, and pathway enrichment all coupled to analyses-oriented visualizations for direct interpretation. We demonstrate NAViFluX through three *Escherichia coli* case studies: (1) carbon source-dependent metabolic rewiring, where flux distributions across central metabolic pathways are compared interactively; (2) pathway-level interpretation of gene essentiality and synthetic lethality, translating knockout simulation results into visual pathway maps; and (3) metabolic engineering for enhanced carbon fixation, illustrating how NAViFluX supports iterative model-guided design cycles. Across these cases, NAViFluX enables experimental biologists to move fluidly between numerical results and pathway-level interpretations a capability currently absent from existing GSMN tools. NAViFluX is freely available as a standalone, open-source tool, broadening access to GSMN-based modelling for the wider systems biology and biotechnology community.

Keywords: genome-scale metabolic networks, flux balance analysis, metabolic modelling, visualization, metabolic engineering

P13

Thermodynamic energy constraints shape enzyme sequence and active-site geometry: evidence from methanogenic archaea across the energetic spectrum of life

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Poster presentation

How low can life’s energy budget go, and what molecular signatures does extreme energy limitation leave in the enzymes that sit at the metabolic bottleneck? We address this question using methyl-coenzyme M reductase (McrA) — the universal, single-copy terminal enzyme of all methanogenesis pathways — as a molecular readout of thermodynamic adaptation. Marine sediment methanogens operate at cellular power budgets of $\sim 10^{-2}$ W per cell, with free energy yields of only -20 to -40 kJ mol⁻¹ per reaction; human gut methanogens perform the same biochemistry at effectively saturating substrate concentrations. These two environments share phylogenetically related organisms but differ by several orders of magnitude in available energy flux, making them a natural experiment in the kinetics and thermodynamics of life at the energetic edge. We assembled a dataset of 298 McrA sequences from metagenome-assembled genomes (MAGs) — 108 from marine sediment, cold seeps, and abyssal plains, 190 from human gut microbiomes — and asked whether the two energetic regimes are distinguishable at the level of enzyme sequence and predicted three-dimensional structure. The answer is yes, and more clearly than expected for one of the most conserved enzymes in biology. Centred log-ratio (CLR) analysis of amino acid frequencies reveals significant compositional differences in 14 of 20 residue types after Bonferroni correction. A logistic regression classifier trained on amino acid dipeptide (2-mer) frequencies correctly assigns 61 of 62 sequences to the right environment (98% accuracy). AlphaFold2-predicted structures reveal that gut McrA active sites are significantly smaller ($-4,385$ Å³, FDR < 0.05), more compact, and more geometrically pre-organised than their sediment counterparts — structural properties consistent with selection for high catalytic turnover (k_{cat}) under substrate-saturating conditions in the gut, versus selection for tight substrate binding (low K_m) under the near-zero substrate concentrations of deep sediment. Beyond the enzyme itself, these results speak

to a broader systems-level question: do the molecular signatures we observe reflect active evolutionary specialisation — organisms accumulating adaptive changes in response to thermodynamic pressure — or ecological filtering, where energy-limited environments simply retain lineages whose ancestral biochemistry happened to be compatible with low-flux conditions? A phylogenetic framework built from the same dataset allows us to begin partitioning these two contributions. The answer matters because it determines whether thermodynamic constraints act as a forge, actively reshaping enzyme kinetics from the bottom up, or as a sieve, selecting among pre-existing molecular variation from the top down. Either way, the results lay the groundwork for a quantitative framework connecting environmental energy flux directly to molecular kinetic parameters — a systems biology of the energetic limits of life.

Keywords: methanogenesis, enzyme kinetics adaptation, energy limitation, AlphaFold2 structural analysis, machine learning sequence classification

P14

Modular response analysis reveals distributed control of insulin sensitivity in C2C12 skeletal muscle cells.

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Poster presentation

Type 2 diabetes (T2D) is a major global health challenge characterised by impaired insulin sensitivity in key metabolic tissues, including skeletal muscle. As skeletal muscle accounts for the majority of insulin-stimulated glucose uptake, dysregulation of the cellular processes governing glucose uptake in this tissue plays a central role in the development of insulin resistance. Insulin-stimulated glucose uptake arises from the coordinated interaction of multiple pathways, including insulin signalling, glucose transporter translocation, and intracellular glucose metabolism. Because these processes are tightly coupled, determining their relative contributions to impaired insulin responsiveness remains a significant challenge.

In this study, we combined experimental measurements with mathematical modelling to investigate the insulin sensitivity in skeletal muscle cells. The mathematical model consists of three interconnected modules: insulin signalling, glucose transport, and glucose metabolism. Experiments were performed using C2C12 mouse skeletal muscle cells in which an insulin-resistant state was induced, enabling system behaviour to be quantified across a range of insulin concentrations under both insulin-sensitive and insulin-resistant conditions.

To quantify how control was distributed between the three modules, we applied modular response analysis, which enabled the estimation of the individual responses of each module in response to insulin and how the responses of each module contribute to the global response of the whole system. While experimental observations suggested that defects in glucose transport dominate under insulin-resistant conditions, the modular analysis revealed that all three modules contribute to the overall reduction in insulin sensitivity. Moreover, the relative contributions of the modules varied as a function of insulin concentration, indicating that control over glucose uptake is distributed across the network and dynamically shifts with the input signal.

Keywords: Insulin resistance, Type 2 Diabetes, Skeletal muscle, Modular response analysis

P15

Reconstruction of context-specific genome-scale metabolic models of mammalian cells: development of a robust protocol

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Poster presentation

Genome-scale metabolic models (GEMs) are widely used in systems biology and precision medicine to study complex biological processes. The integration of high-throughput omics data enables the reconstruction of context-specific models; however, selecting appropriate model extraction methods (MEMs) and their parametrisation remains a major challenge, often resulting in inconsistent or even contradictory outcomes across studies. In this work, we present a systematic protocol for the reconstruction and evaluation of context-specific GEMs, aimed at identifying the most suitable MEM and its configuration for a given dataset. The proposed framework integrates multiple analytical approaches, including principal component analysis (PCA), assessment of variance explained by experimental factors, model similarity analysis using Jaccard indices, and metabolic activity estimation through flux sampling. The protocol was applied to diverse biological contexts, including transcriptomic data from Cyp51 knockout mouse models, COVID-19 datasets, and hepatocellular carcinoma (HCC) patient-specific models. Our results confirm that the choice of MEM is a major determinant of model structure, variability, and biological interpretability. Different MEMs produced models with substantial differences in size, reaction content, and enrichment of metabolic subsystems, even when based on identical datasets and reference models. In the context of COVID-19, we demonstrate that MEM selection critically affects the identification of biologically relevant metabolic pathways. Specifically, tINIT and GIMME approaches showed an improved ability to preserve biologically meaningful variability and to identify metabolic alterations consistent with clinical observations, such as dysregulation of lipid, cholesterol, and vitamin metabolism. Overall, our results highlight that relying on a single MEM or parameter setting can lead to incomplete or misleading biological interpretations. We therefore propose a standardised protocol that systematically evaluates multiple MEMs and parameter configurations to ensure robust and biologically relevant model reconstruction. This approach provides a generalisable framework for GEM-based analysis of omics data and supports more reliable applications in systems medicine, including biomarker discovery and precision medicine.

Keywords: genome-scale metabolic models, model extraction methods, omics data integration

P16

pyPGLM, a toolbox for the fast contextualization of logical networks

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Poster presentation

Logical network models are widely used to study cellular signalling because they retain mechanistic interpretability while remaining substantially more tractable than fully specified ordinary differential equation models. They are therefore well suited for analysing perturbation-response data in settings where prior biological knowledge is available but quantitative kinetic information is incomplete. However, translating prior-knowledge logical networks into data-informed, context-specific models remains a major practical challenge. In particular, fitting such models to quantitative measurements, assessing uncertainty, and comparing regulatory structure across related biological contexts are still difficult to do within a unified and accessible computational framework. Here we present pyPGLM, a Python toolbox for the construction, contextualization, fitting, and analysis of Probabilistic Graphical Logical Models for signalling networks. pyPGLM combines prior network topology with experimental perturbation data to estimate model parameters and simulate condition-specific responses under stimulation or inhibition. The toolbox supports import of network and measurement data, deterministic and Bayesian parameter inference, model validation, held-out prediction, uncertainty quantification, and downstream analysis of inferred regulatory structure. It also provides tools for multi-context inference through globalized models and mixed regularization schemes, allowing related datasets to be analysed jointly while distinguishing shared from context-specific interactions. We demonstrate the use of pyPGLM on synthetic benchmarks and on a real signalling application. These examples show how the toolbox can be used to fit signalling models from perturbation-response data, evaluate predictive performance on unseen conditions, quantify parameter uncertainty, and identify regulatory differences across biological contexts. By integrating model contextualization, predictive evaluation, uncertainty analysis, and

efficient post-fit investigation in a single environment, pyPGLM provides a practical framework for extracting both qualitative and quantitative insight from signalling data and for generating biologically testable hypotheses.

Keywords: signaling, logical network model, probabilistic modeling

P17

A digital tomato: modelling resource allocation in young growing fruit

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Poster presentation

Given its widespread consumption worldwide, the tomato serves as a model organism for fleshy fruits. Furthermore, with the advent of high-throughput analytical methods, omics data are now available, and the tomato genome has been sequenced (The Tomato Genome Consortium, 2012). Constraint-based modelling can be used to estimate metabolic fluxes at the genome-wide level, and metabolic models of tomato have been reconstructed for this purpose (Yuan et al., 2016, and Gerlin et al., 2022). My thesis goes beyond this framework by applying Resource-Balance Analysis (RBA, Goelzer et al., 2024) to predict agronomically relevant phenotypes of tomato. Unlike conventional GEMs, RBA explicitly incorporates the cellular allocation of resources to all protein families, including those involved in enzymes but also in the main cellular processes (transcription, translation, protein turnover) as well as the space constraints imposed by sub-cellular compartments. The model will be calibrated with available omics data—transcriptomics, proteomics, and metabolomics (Belouah et al. 2020)—to generate phenotype simulations that reveal the mechanistic determinants of fruit growth and suggest strategies for improving plant performance.

To start, I will use the existing tomato model (Gerlin et al. 2022) to refine enzyme annotations and rebuild the relevant molecular machineries by leveraging orthologs from *Arabidopsis thaliana*. Once the network topology is satisfactory and the descriptions of enzymatic complexes and subcellular compartment densities are accurate, the model will serve to simulate and predict metabolic fluxes in young tomato fruits under varying nutritional regimes and temperature scenarios. Prior to that, I have already designed a fruit-specific biomass reaction and validated it with flux-balance analysis, providing an initial assessment of the model’s relevance. The resulting resource-balanced model will provide a quantitative, genome-wide view of how metabolic and cellular resource allocation shapes tomato fruit development. By linking omics-derived parameters to observable phenotypes, the framework aims to identify bottlenecks and leverage points for breeding or engineering more resilient and higher-yielding tomato cultivars.

Keywords: Resource Balance Analysis, Metabolic modelling, fleshy fruit, Plant system biology

P18

Development of an interactive web application for constraint based modelling

Zuhtu Tutar, Saad Rasool, Kate Meeson, Jean-Marc Schwartz

Poster presentation

Genome-scale metabolic models mathematically reconstruct an organism’s metabolic network to simulate biological phenotypes. Flux Balance Analysis (FBA) is the primary method used to interrogate these models. It relies on a constraint-based optimisation approach to predict metabolic flux distributions by assuming an internal pseudo-steady state. Because metabolic networks are mathematically underdetermined, FBA requires a defined objective function, such as biomass maximisation, to identify optimal flux distributions within boundaries set by environmental and physiological capacities. While established software suites provide advanced analytical capabilities, they often require programming proficiency or familiarity with underlying linear programming frameworks, creating a barrier for non-computational researchers. Existing platforms like OptFlux, KBase and MORFlux provide sophisticated tools but are either tailored towards expert pipelines or require manual parameter configuration.

To address this, this project presents a graphical user interface designed to simplify FBA simulation configuration and execution. Built in Python, the application uses COBRApy for constraint-based modelling calculations and Streamlit for the web interface. To ensure responsive user interactions, the system includes a preprocessing pipeline that parses Systems Biology Markup Language (SBML) files, minimising the computational overhead of real-time model manipulation within the browser.

The application allows users to execute FBA simulations, adjust constraints and visualise flux distributions without writing code or editing raw model files. While the tool prioritises ease of use over the broader flexibility of command-line software, it provides accessible core constraint-based analysis functions. This project demonstrates that complex metabolic models can be effectively abstracted through interface design, lowering the technical entry barrier for metabolic research and providing a structured framework for future multi-omics integration.

Keywords: Genome-scale metabolic model, Constraint-based analysis, Flux balance analysis

P19

Subtype-Specific Gene Expression and Proliferation Dynamics in 2D and 3D High-Grade Serous Ovarian Cancer Cell Cultures

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Poster presentation

High-grade serous ovarian cancer (HGSOC) is the most lethal gynaecological malignancy, largely due to late diagnosis and tumor heterogeneity. Accurate preclinical modelling of HGSOC biological complexity is essential to improve translational research outcomes and therapeutic development; however, traditional 2D models have limited translational relevance. We therefore compared the morphological, proliferative, and molecular characteristics of four HGSOC cell lines (OVCAR-4, OVSAHO, COV362, and Kuramochi) in 2D versus 3D culture environments. To support systematic interrogation of 3D models, we developed reproducible protocols for 3D spheroid generation and optimized a dissociation method for downstream analysis. We observed significant differences in cellular behaviour, morphology, cell cycle regulation, and gene expression. Kuramochi cells showed upregulated EMT markers WNT11B and VIM, suggesting an increased invasive phenotype, i.e., enhanced epithelial–mesenchymal transition and signalling pathways. In OVSAHO cells, MMP2 was significantly downregulated while VEGFA was upregulated, highlighting alterations in matrix remodelling and angiogenesis, characterizing this cell line as proliferative rather than invasive. COV362 cells showed an initial decrease followed by an increase in KI67 expression. Downregulation of BRCA1 and KI67 indicates reduced cell proliferation in 3D environments. Proliferation kinetics were also altered in 3D environments: Kuramochi and OVCAR-4 adopted a more quiescent phenotype, while COV362 remained more proliferative with significant KI67 overexpression. These proliferation dynamics were confirmed with immunocytochemistry. Alignment of expression data showed that different cell types align with distinct HGSOC subtypes: OVSAHO with immunoreactive, OVCAR4 with mesenchymal and differentiated, COV362 with differentiated and proliferative, and Kuramochi with proliferative subtype. The described 3D models can serve as high-throughput platforms for drug testing and functional studies, as well as for studying the complex molecular dynamics of ovarian cancer. Moreover, co-culturing systems can enhance their translational potential for the development of more effective therapeutic strategies.

Keywords: tumor microenvironment, advanced cellular models, proliferation dynamics, 3D cell culture, epithelial–mesenchymal transition

P20

Investigating metabolic reprogramming in pancreatic ductal adenocarcinoma using genome-scale metabolic modelling

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Poster presentation

Pancreatic ductal adenocarcinoma (PDAC), a cancer type that arises in the pancreatic ducts, remains one of the most lethal malignancies, with a mortality rate approaching 95%. This in large part stems from the asymptomatic nature of early-stage PDAC and the lack of effective screening methods. Because of this, diagnosis often occurs at advanced stages, limiting treatment options and contributing to poor patient outcomes [1]. Thus, a deeper understanding of the metabolic alterations associated with PDAC is crucial for improving both diagnostics and treatment of the disease. In this study, we utilized publicly available bulk transcriptomic data from PDAC patients to construct context-specific genome-scale metabolic models (GEMs) using the fast task-driven integrative network inference for tissues (ftINIT) algorithm [2]. We systematically evaluated multiple input combinations to determine the optimal parameters for generating biologically relevant models. These were analyzed using various statistical and bioinformatical approaches. Furthermore, using the generated models, we investigated the metabolic impact of melanoma associated antigen A3 (MAGE-A3) overexpression in pancreatic cancer cells. While MAGE-A3 is known to contribute to tumorigenesis and its expression in cancer cells correlates with poor clinical outcomes [3], its role in cancer cell metabolism remains largely unexplored. By characterizing the metabolic consequences of MAGE-A3 upregulation, we aimed to provide novel insights into its impact on pancreatic cancer metabolism, paving the way for further research into its role in disease progression. [1] Sarantis, P.; Koustas, E.; Papadimitropoulou, A.; Papavassiliou, A. G.; Karamouzis, M. V. Pancreatic Ductal Adenocarcinoma: Treatment Hurdles, Tumor Microenvironment and Immunotherapy. *World J Gastrointest Oncol* 2020, 12 (2), 173–181. [2] Gustafsson, J.; Anton, M.; Roshanzamir, F.; Jörnsten, R.; Kerkhoven, E. J.; Robinson, J. L.; Nielsen, J. Generation and Analysis of Context-Specific Genome-Scale Metabolic Models Derived from Single-Cell RNA-Seq Data. *Proc Natl Acad Sci U S A* 2023, 120 (6), e2217868120. [3] Florke Gee, R. R.; Chen, H.; Lee, A. K.; Daly, C. A.; Wilander, B. A.; Fon Tacer, K.; Potts, P. R. Emerging Roles of the MAGE Protein Family in Stress Response Pathways. *J Biol Chem* 2020, 295 (47), 16121–16155.

Keywords: Transcriptomics, Context-specific genome-scale metabolic models, Fast task-driven integrative network inference for tissues algorithm, MAGE-A3 protein

P21

The role of fungal LysM effectors in plant immunity suppression and microbiota manipulation

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Poster presentation

Proteins that comprise lysin motifs (LysMs) substantially contribute to interactions between plants and microorganisms through their ability to bind carbohydrate polymers containing N-acetylglucosamine (GlcNAc) residues such as peptidoglycan or chitin and their derivatives. Chitin, a major component of fungal cell walls, acts as a microbe-associated molecular pattern (MAMP) and can be perceived by plants through LysM domains present in receptor complexes, resulting in immune activation. One fungal strategy to suppress this chitin-induced immunity involves the secretion of LysM effector proteins, molecules containing no other protein domain than the LysM domain. These effectors can

perturb chitin-induced immune signaling through multiple mechanisms, including scavenging of free chitin oligomers, shielding of the fungal hyphae and potentially through interfering with plant chitin recognition receptors. Beyond their role in suppressing chitin-induced immune signaling, LysM effectors may also display antimicrobial activity through binding to peptidoglycan, the main component of bacterial cell walls, thereby potentially modulating intermicrobial competition and facilitating invasion. Importantly, as these different effects of LysM effectors are mediated by one, and the same, binding site in the effector molecule, they cannot be separated, e.g. through mutation and their individual contributions to colonization success are not known. In order to understand how different functions of single LysM effectors contribute to fungal colonization and infection success, a mechanistic modeling approach will be used to build a theoretical framework to test and discriminate different hypotheses. A simple mechanistic model of the signaling pathway has been developed to simulate and discriminate different effects of LysM effectors on chitin-induced immunity. Moreover, a population dynamics model has been constructed to simulate how the composition of a small synthetic microbial community may be affected by antimicrobial LysM effectors. These two models will be integrated into a unified framework to address questions such as whether a single LysM effector mechanism is sufficient to support successful host colonization, how LysM effector concentration influences the relative contributions of different suppression mechanisms, and how immune suppression and intermicrobial competition interact during infection. With our models we provide a framework in which the effects of different suppression mechanisms during infection can be quantified. We envisage that our models are highly useful to provide a clearer understanding of the dynamics at the infection site.

Keywords: plant immunity, mechanistic modeling, microbial community dynamics

P22

ANCHORS - Attention-based Neural Computation and Hybrid model Optimization for Reconstruction of Complex Dynamic Biological Systems

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Poster presentation

Gene Regulatory Networks (GRNs) provide a formal framework to describe dependencies and interactions between genes and their products, and accurate inference of large-scale GRNs combined with reliable prediction of temporal dynamics remain a challenging problem. Gene expression datasets are often high-dimensional, where the number of experiments is typically much smaller than the number of genes. In addition, gene expression profiles are inherently stochastic and contain a certain degree of noise. Existing approaches for inference and modelling of GRNs typically separate structural inference from dynamic prediction. Ordinary differential equation models normally require predefined topology and kinetic parameters to simulate gene expression dynamics, whereas data-driven inference approaches reconstruct static GRN structures based on data dependencies and various statistics. This discrepancy limits the scalability, interpretability, and predictive power of inferred models.

In our work, we aim to transcend this limitation by introducing a novel hybrid encoder-decoder framework, designed to unify topological inference and prediction of temporal dynamics. In our architecture, the latent space explicitly represents a directed adjacency matrix, which corresponds to the GRN topology. Temporal gene expression data are processed through parallel LSTM units and self-attention mechanisms, generating gene-wise feature representations that capture short-term temporal dependencies. These representations are combined to construct a latent adjacency matrix. A multi-stage graph neural network decoder then utilizes this topological knowledge to predict the rate of change in gene expression at subsequent time points, effectively approximating the underlying differential equations and reconstructing continuous temporal trajectories from time series data.

Since GRNs exhibit similar general topological characteristics, such as sparsity, short average path lengths, and enrichment of network motifs, we utilize topological anchoring through structural priors derived from the triadic census and other topological properties. The latent adjacency matrix is optimized using a multi-component loss function that combines expression-level prediction error with latent-space regularization, sparsity-inducing binary regularization term, and triad-based struc-

tural constraints that enforce biologically plausible models. A multi-stage training strategy, including adjacency matrix pretraining (partial-correlation or multivariate lasso regression) and utilization of constrained decoding, which ensures that the learned topology remains interpretable and robust while preserving high predictive accuracy.

We have implemented a preliminary prototype in Python with the PyTorch library. Based on preliminary results, our model can reliably predict gene regulatory network dynamics for small-scale networks comprising up to 64 genes with a prediction error of a few percentage points.

Keywords: Gene Regulatory Networks, Gene Regulatory Network inference, Dynamic modeling of biological systems, Attention-based encoder-decoder, Graph Neural Networks

P23

Metabolic-isotopic model of sulfite reduction: Environmental and evolutionary implications

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Poster presentation

Microbial metabolism drives the transformation of S across its full range of oxidation states (from -2 to $+6$), tightly coupling the S cycle to those of C, O₂, and Fe. Sulfur isotope fractionation associated with these transformations is recorded in dissolved and mineral reservoirs, providing a quantitative window into Earth-system function. A central feature of this record is the muted variability of sedimentary pyrite $\delta^{34}\text{S}$ values during the Archean (before 2.5 billion years ago), rarely exceeding $\sim 20\text{‰}$ relative to coeval seawater sulfate, in contrast to broader ranges observed later in Earth history ($\sim 40\text{--}50\text{‰}$ from 2.5 to ~ 0.7 billion years ago, and $\sim 60\text{--}70\text{‰}$ thereafter). The muted range of Archean $\delta^{34}\text{S}$ has traditionally been attributed to the effect of low seawater sulfate on microbial fractionation during dissimilatory sulfate reduction (DSR) and more recently to the effects of low sulfate on the “openness” of reaction and transport in sediments. The possibility that the muted range instead reflects inherently limited fractionation of an evolutionarily simpler sulfite-reducing pathway has not been quantitatively explored. Phylogenetic and comparative genomic analyses support this view, indicating an archaeal origin of the minimal Dsr protein set (DsrABCMK(N)), with a primary sulfite reduction function. Before atmospheric oxygenation drove the accumulation of seawater sulfate, volcanic SO₂ degassing and speciation in seawater would have plausibly made sulfite an accessible oxidized S substrate, potentially supporting early sulfite-reducing microbial communities. To address this, we adapted the published genome-scale metabolic model of the sulfate reducer *Desulfovibrio vulgaris* Hildenborough (iJF744). We first modified the Dsr-catalyzed reduction of sulfite to sulfide in accordance with the latest understanding of this reaction, splitting it into two sequential steps – initial reduction of sulfite to a DsrC-bound trisulfide by the DsrAB complex, and subsequent reduction of the trisulfide to sulfide coupled to electron recycling through the DsrMK complex. We then truncated the full sulfate reduction network to a sulfite-reduction core and added a sulfite uptake step. Flux balance analysis applied to this truncated network allows us to quantify how environmental conditions influence intracellular fluxes, reaction reversibility, and S isotope fractionation. Over a plausible range of sulfite and sulfide concentrations in early Archean seawater, the predicted net S isotope fractionation spans $\sim 10\text{--}30\text{‰}$, clustering near $\sim 20\text{‰}$. This limited range reflects sulfite reduction operating far from thermodynamic equilibrium under early Earth conditions, reducing reaction reversibility and limiting near-equilibrium S isotope effects. The predictions align with the observed microscale S isotope variability in Archean marine pyrite. Thus, in addition to the effects of sulfate limitation on S isotope fractionation during DSR and/or on sulfate transport and reaction, the muted record could stem from limited S isotope fractionation in the sulfite-reduction pathway. The step increase in isotopic variability near the Archean-Proterozoic boundary may, therefore, record the evolutionary transition from sulfite reduction to the complete sulfate reduction pathway.

Keywords: Metabolic modelling, Isotopes, COBRA toolbox, FBA, Sulfite reduction

P24

Integration of omics data for response prediction to neoadjuvant treatment in resectable Non-Small Cell Lung Cancer

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Poster presentation

Neoadjuvant (NA) therapy, chemotherapy or chemoimmunotherapy given before surgery, has shown promise in improving survival in patients with operable Non-Small Cell Lung Cancer (NSCLC) by shrinking tumors and targeting hidden cancer cells, thereby increasing the chances of complete surgical removal and reducing recurrence. However, responses vary widely: while some patients experience major benefit, others gain little or suffer serious side effects, emphasizing the urgent need for reliable biomarkers to predict treatment outcomes and toxicity. Currently, there is no robust strategy to accurately identify patients who are most likely to respond favourably to NA therapy or those at higher risk of treatment-related toxicity, posing a challenge for personalized treatment approaches. This project aims to identify tumor and blood-based biomarkers linked to response and adverse events using an integrated multi-omics approach that combines genomics, epigenomics, transcriptomics, proteomics, and metabolomics data. Alongside molecular profiling, we will incorporate clinical, lifestyle, and nutritional factors to build predictive models through advanced bioinformatics and machine learning. Responsive and non-responsive cases will be studied to identify biomarkers or other signatures in pre-treatment samples that can be linked with therapy response and can serve as biomarkers for predictive modelling. The mechanistic nature of systems biology approach in the analysis of sample-specific genome-scale metabolic models (GEMs) enable analysis of functional impact of particular changes: can the observed change in the flux of one metabolic subsystem or pathway be fully or partly compensated by another metabolic subsystem and how that depends on the availability of metabolites and if that is limited by some cellular resources. Different metabolic strategies will be identified within responding and non-responding sample groups. By identifying molecular signatures that distinguish responders from non-responders and those prone to toxicity, we aim to create a predictive framework to personalize NA therapy. Ultimately, this work supports more precise patient selection, enhance treatment effectiveness, minimize toxicity, and contribute to biomarker-driven strategies that improve outcomes and advance personalized medicine in NSCLC.

Keywords: multi-omics, genome-scale metabolic modeling, biomarkers, machine learning

P25

TRIM-Flux: Integrating Metabolic Flux into Multimodal VAEs for Predicting T-cell State Transitions in Cancer Immunotherapy

Aljaž Kos, Ana Halužan Vasle, Miha Moškon

Poster presentation

Cancer immunotherapy holds great promise, yet patient outcomes remain highly unpredictable, with some individuals responding remarkably well while others experience little to no benefit. A key determinant of this variability is the functional state of T cells. As treatment progresses, T cells can become exhausted, losing their ability to fight cancer. Predicting the post-treatment state of a patient's T cells before therapy could fundamentally change clinical decision-making. Recent advances in generative AI have made such predictions possible by learning from single-cell genomic data. However, these models capture only the transcriptional dimension of T-cell biology, overlooking the profound metabolic rewiring that accompanies exhaustion. We present TRIM-Flux, an extension of the TRIM multimodal conditional variational autoencoder – VAE developed by He et al., 2026. The proposed framework integrates scRNA-seq data, T-cell receptor (TCR) clonotype, and metabolic flux data to predict T-cell state transitions from pre-treatment blood samples to post-treatment tumor. Metabolic fluxes are computed via flux sampling on the Human1 genome-scale metabolic model conditioned on single-cell RNA counts from HNSCC dataset (GSE200996, 27 patients, 146,776 cells). The resulting cell-specific flux vectors are fed into an encoder-decoder branch that merges with the existing RNA

and TCR branches into a shared latent space. All three branches are jointly conditioned on learned embeddings for tissue, treatment stage, and patient. We evaluate three model variants — RNA+TCR, Flux+TCR, and RNA+TCR+Flux — using leave-one-patient-out cross-validation across 27 HNSCC patients. Performance is assessed by clonal expansion prediction and post-treatment transcriptional state recovery. Preliminary results indicate that metabolic flux captures aspects of T-cell functional heterogeneity not fully reflected in transcriptomic data alone, supporting the broader integration of constraint-based metabolic models into single-cell deep generative frameworks.

Keywords: GEM, scRNAseq, variational auto encoder, cancer, immunotherapy

P26

Using the ReStoRunT idea to document provenance in transformation of large, complex Excel workbooks

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Poster presentation

ReStoRunT is an SOP and software for documenting changes in Excel format. It permits REcording, STOring, reRUNning and Tracing changes in Excel and other spreadsheet files. The basic idea is to use the basic formula functionality of Excel to manipulate *references* as opposed to just the values in the sheets. A sheet made up of references can then be used as a transformation program. A publication, as well as SOP document at <https://github.com/mertova/ReStoRunT> describe it in-depth.

The initial motivation was to use ReStoRunT on Excel workbooks of ongoing experiments, where it was designed to facilitate bringing machine-related experimental Excel files into a common shape. In this presentation we focus on Excel as a staging zone for data transformations and the use of the ReStoRunT concept for that: In our use case, clinicians prepare their data for import into a REDCap database. The *local format* and the *import format* were very different, as the local format was geared towards readability, and the REDCap import format is geared towards import flexibility.

This use case shows well, how ReStoRunT is also useful as a debugging and documentation tool for even very complex transformations, documenting the provenance of outcomes within the transformed workbook. This guarantees that the transformed sheet stays in the same document as the initial sheet, thus assuring that the documentation of the transformation does not get lost. We see this as a key facilitator for FAIRness, as in the times of generative AI the documentation of precise sources becomes more and more important.

We will highlight strengths and limitations of this approach, as well as efforts to increase adoption by software integration.

Keywords: Spreadsheets, Provenance, Transformation, documentation, FAIR

Metabolic cross-feeding and inter-species dynamics

Chaired by: Frank Bruggeman

O29

Metabolic games in an autotroph-heterotroph consortium: eco-evolutionary analysis of cooperative, private and cheater exoenzyme strategies

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Oral presentation

Synthetic microbial consortia offer a controlled setting to study how ecological and evolutionary forces shape community structure. Here we present a mathematical framework for a cross-kingdom autotroph-

heterotroph system in which a sucrose-secreting cyanobacterium feeds a heterotrophic community. We model three heterotrophic metabolic strategies- public metabolizing, private metabolizing and cheating and analyse how their metabolic interactions shape coexistence and competition. The framework combines generalized Lotka-Volterra dynamics, Michaelis-Menten kinetics and evolutionary game theory to represent nutrient exchange and frequency-dependent fitness. Laboratory-inspired eco-evolutionary simulations allow strategies to switch between generations, mimicking mutation or phenotypic plasticity. These dynamics reveal parameter regimes and thresholds separating collapse, dominance and coexistence, and show how growth advantages and switching rates drive shifts in community composition and robustness of this cross-kingdom consortium. Together, these results provide design rules for constructing stable synthetic communities under ecological and evolutionary constraints. To make the model accessible and reusable, we deploy it in mxlweb, a browser-based interface for ODE models, where users can vary parameters and initial conditions, run simulations and explore “what-if” scenarios without installing software, enabling rapid exploration and sharing of model-based insights.

Keywords: Metabolic interaction, autotroph -heterotroph microbial community, modelling synthetic community, ecological and evolutionary dynamic , browser-based interface for ODE models

O30

Fermentation revisited: facultative anaerobes and the rate-yield trade-off in the gut microbiome

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Oral presentation

Microbial growth is widely thought to obey a rate-yield trade-off: cells either grow fast and dissipate energy (e.g. fermenting *E. coli*) or grow efficiently by fully respiring substrate (Pfeiffer 2001). This trade-off has further been linked to social behavior, with fast growth interpreted as “cheating” and efficient growth as “cooperation” in structured communities such as biofilms (Kreft 2004). In natural microbial ecosystems, however, the trade-off appears far less universal and may primarily structure the fast-growing fraction of communities (Lipson 2015). Most supporting evidence comes from model organisms under aerobic conditions, yet fermentation, in Pasteur’s sense of “life without oxygen”, predominates in anoxic habitats. This raises the question of where genuinely fast-growing organisms occur in nature and whether the rate-yield trade-off is relevant there. The mammalian gut microbiome offers a paradoxical test case. The colon is kept anoxic by the host, sustaining a dense anaerobic food web whose fermentation products supply roughly 10% of host energy demand and thereby affect host fitness. Strikingly, fermentation in this system appears to be the cooperative, health-associated strategy, whereas respiration by facultative anaerobes is associated with dysbiosis and disease (Byndloss 2017), the opposite of the classical rate-vs-yield mapping. Here, we investigate the rate-yield trade-off in gut microbiomes by combining growth-trait data from experimental databases with a mathematical model of fermenter-facultative anaerobe dynamics. We find that gut fermenters are slow-growing and efficient whereby O_2 -consuming facultatives are fast-growing cheaters, inverting the textbook association between fermentation, fast growth, and waste. These results recast the rate-yield trade-off in an ecological and host-associated context, with implications for one of the most consequential microbiomes in biology.

Pfeiffer 2001: Cooperation and competition in the evolution of ATP-producing pathways. Science <https://doi.org/10.1126/science.1058079> Kreft 2004: Biofilms promote altruism. Microbiology <https://doi.org/10.1099/mic.0.26829-0> Lipson 2015: The complex relationship between microbial growth rate and yield and its implications for ecosystem processes. Frontiers in Microbiology <https://doi.org/10.3389/fmicb.2015.00615> Byndloss 2017: Microbiota-activated PPAR- signaling inhibits dysbiotic Enterobacteriaceae expansion. Science <https://doi.org/10.1126/science.aam9949>

Keywords: microbial physiology, rate vs. yield tradeoff, gut microbiome

Butyrate production is shaped by microbial interactions in an infant synthetic community

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Oral presentation

In early life, the microbiome undergoes drastic transitions driven by dietary changes and exposure to external microbes. Breastfed infants typically develop a Bifidobacterium-rich microbiome, in which human milk oligosaccharides (HMOs) shape community composition and, thereby, short-chain fatty acid (SCFA) production. In our eight-species infant Bacterial Community (iBaCo), different HMO substrates led to shifts in species abundance and SCFA levels. Butyrate, for example, has been linked to epithelial barrier maturation and immune development, and reduced early-life butyrate availability has been associated with later inflammatory or allergic outcomes. Because it is difficult to test SCFA production via bacterial fermentation in vivo and because in vitro experiments are time-consuming, we use iBaCo as a benchmark to assess whether genome-scale metabolic models (GEMs) can explain the potential community interactions underlying the experimentally observed SCFA levels.

We developed a pipeline that generates species-specific GEMs from bacterial genomes and mono-culture growth data across HMO conditions. Curated models were first used with flux analysis techniques to predict mono-culture SCFA secretion based on carbon-source-specific growth fitting. Next, the eight GEMs were integrated into two- and three-species community models to screen the predicted interaction landscape for candidate cross-feeding metabolites that positively influence butyrate production. Selected species combinations were then simulated using dynamic flux balance analysis to capture time-dependent growth and metabolite exchange.

Under matched external conditions, curated iBaCo GEMs reproduced experimental mono-culture SCFA secretion patterns more accurately than reference models. In two-species simulations containing the only butyrate producer, *Anaerostipes caccae*, and *Bifidobacterium longum* subsp. *infantis*, we observed cross-feeding of acetate, lactate, and monosaccharides released by *B. infantis*, consistent with experimentally reported interactions. Similar interactions were observed for other Bifidobacteria. Importantly, this suggests an interaction-dependent mechanism of growth and butyrate production, since *A. caccae* cannot directly degrade HMOs. Moreover, simulations highlighted that negative interactions could arise between *Bacteroides fragilis* and *A. caccae*, inhibiting butyrate secretion, but that these were HMO-dependent and in some cases a combination of cross-fed metabolites alleviated this inhibition. In three-species simulations where *B. fragilis*, *A. caccae*, and a Bifidobacterium were present, *B. fragilis* scavenged the cross-feeding metabolites, and butyrate production was not observed.

Together, these results suggest that butyrate production in HMO-driven infant microbial communities may depend on substrate-specific cross-feeding between primary HMO degraders and the butyrate producer *A. caccae*. More broadly, combining metabolic modeling with defined synthetic community experiments provides a framework for predicting how dietary substrates shape community composition and metabolite production, and for prioritizing follow-up experiments to understand community interactions.

Keywords: cross-feeding, genome-scale metabolic modeling, community dynamics, butyrate

Optimizing the resource allocation between biochemical defence and counter-counter defence in pathogenic and trophic interactions. Steady-state analysis

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Oral presentation

In many interactions between hosts and pathogens or plants and herbivores, the attacked organism produces a chemical compound to defend itself. The attacker often responds by producing a counter-

defence, such as an enzyme that can degrade the defence chemical. Sometimes, the defender escalates this arms race by producing another chemical, a counter- counter defence, that can inhibit the degrading enzyme. Many of these interactions attain at steady-state. For example, IgA1 antibodies can kill pathogenic bacteria, like *Streptococcus pneumoniae*. To counter that, *S. pneumoniae* can produce a specific IgA1 protease as a counter defence to the antibodies. The host, in turn can synthesize IgG antibodies, which can inhibit these proteases. In this theoretical study, we analyse under which conditions it is favourable to invest resources into the production of a counter-counter defence and, if so, to what extent. A mathematical model, based on enzyme kinetics was developed. For this model, we derived the equation for the steady-state concentration of the defence chemical and solved a resource allocation problem, with the goal of maximising this concentration. The calculations revealed that only if the inhibitor shows certain properties it is favourable to develop a counter-counter defence. We also found that it depends on the amount of available resources, whether the production of an inhibitor is beneficial. However, it is never optimal to invest more resources into the inhibitor than into the toxin, provided that their costs are approximately equal. The results can be of interest for calculating the optimal mixing ratios of antibiotics and beta-lactamase inhibitors or other drug combinations that are given continuously for a prolonged time, for example, by continuous infusion.

Keywords: Resource allocation problem, Enzyme kinetics, ODE model, chemical defence, Steady state

Bridging omics and metabolic models

Chaired by: John Hancock

O33

COBRA-k: a novel framework bridging constraint-based and kinetic metabolic modeling

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Oral presentation

Mathematical modeling is key to understanding cellular metabolism. Two common metabolic modeling approaches are constraint-based (COBRA) and kinetic modeling. COBRA focuses on the computation of steady-state flux distributions using linear constraints and optimization techniques and proved valuable for studying various properties of genome-scale metabolic networks. However, traditional COBRA models do not incorporate full reaction kinetics and are thus limited regarding quantitative predictions that depend on metabolite concentrations. In contrast, kinetic models are based on kinetic rate laws with metabolite concentrations as state variables. These models offer realistic descriptions and dynamic simulations but require as input kinetic parameters (k_{cat} , K_m) as well as enzyme concentrations (or v_{max} values), which are often unavailable. Here we introduce COBRA-k (COBRA with kinetic constraints), a framework that integrates non-linear kinetic rate laws with linear COBRA constraints to consistently constrain metabolic fluxes, enzyme abundances and metabolite concentrations [1]. Unlike kinetic models, COBRA-k permits free enzyme concentrations and enables flexible exploration of metabolic steady states with optimization techniques, also with incomplete parametrization or simplified rate laws.

COBRA-k models require solving computationally demanding mixed-integer non-linear programs (MINLPs). We found that state-of-the art (global) MINLP solvers fail in finding optimal solutions in larger COBRA-k models. We therefore developed a dedicated iterative algorithm (COBRA-k solver) and implemented it in an open-source Python package. This package also aids in constructing COBRA-k models and retrieving associated kinetic parameters from different databases.

As an application, we constructed and analyzed a large-scale COBRA-k model of *E. coli* comprising all reactions of the central metabolism and major biosynthetic pathways. This analysis demonstrated the validity and effectiveness of the COBRA-k approach. The model predictions agree well with fluxomic, metabolomic and proteomic data and also reproduce the switch from fully respiratory to overflow metabolism for increasing growth rates. The model also provides novel metabolic insights. For example,

it accurately predicts and explains the phenomenon of high intracellular glutamate concentration in *E. coli*.

Overall, COBRA-k combines the flexibility of COBRA with kinetic precision, offering a powerful framework for predictive metabolic modeling and engineering.

[1] Bekiaris PB, Klamt S (2026). COBRA-k: a powerful framework bridging constraint-based and kinetic metabolic modeling. *Science Advances* 12:eaeb3022.

Keywords: Metabolic modeling approaches, Constraint-based and kinetic models, *Escherichia coli*, Theoretical systems biology, Glutamate metabolism

O34

ThermoDB – Metabolic Potentials Under User-Defined Conditions

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Oral presentation

In previous work [1], we have defined a new metabolic thermodynamic reference state of pH = 7, pMg = 3, 99.5% water, with 1 mM each of the additional ‘precursors’ inorganic phosphate, sulphate, ammonium and bicarbonate, and with twin temperatures 37 and 25 °C, ionic strength 0.15 M and mM as concentration unit. This reference state is closer aligned to the state inside living cells, and moreover aligns better than the standard physical-chemical reference state (1 bar for gaseous elements, solids for the other elements, and an activity of 1 for molecules) with conditions frequently used in chemistry in vitro and in silico. Standard chemical potentials can be transformed into ‘metabolic potentials’ by subtracting the chemical potentials of the metabolic precursors from reference chemical potentials.

Here we present ThermoDB, a searchable database of metabolic potentials based on data in the Thermotable Excel file [1], which calculates these potentials from a collection of more than a thousand reference chemical potentials from a variety of literature sources. The database is implemented in Python and, in addition to providing the potentials at the metabolic reference state, allows the calculation of these at user-defined values of pH, pMg, osmolarity, temperature and ionic strength. The calculations are implemented via Legendre transformations for the number of protons, oxygen atoms and Mg²⁺ ions in the species, enthalpy corrections for temperature, and correction for ionic strength using extended Debye-Hückel theory. Moreover, each of the Legendre transformations can be separately selected, allowing the user to retrieve the standard (untransformed) chemical potential, fully transformed metabolic potential, or any other combination (e.g. only H⁺ and Mg²⁺-transformed values). In addition, common biochemical species such as ATP that exist in multiple protonation or Mg-complexation states, are retrievable as ‘blends’, removing non-essential diversity.

The reference metabolic potential corresponds to the molecule’s energetic impact in metabolism under physiological conditions and correlates with its position in a metabolic pathway in terms of gradual cascades that predict flux directions in biochemical networks. The free energy of ATP hydrolysis under cellular conditions also emerges naturally from this reference state. Furthermore, the ThermoDB provides consistent thermodynamic parameters for the construction of kinetic models in systems biology even when these the models describe conditions that deviate from the metabolic reference state in terms of pH, temperature, ionic strength or any of the other input parameters.

[1] Westerhoff, H. V., Bakker, B. M., Bommarius, A. S., et al. (2026), Metabolic thermodynamics: pertinent reference state and energy potentials, *FEBS J.* DOI:10.1111/febs.70415

Keywords: metabolic potential, Gibbs free energy, temperature, ionic strength, pH

O35

From RNA-Seq to Mechanistic Insights: A Unified Pipeline for Context-Specific Metabolic Model Analysis

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Oral presentation

Genome-Scale Metabolic Models (GSMMs) are mathematical representations enabling the analysis of pathway activities, metabolite production or exchange, and essential metabolic genes. To improve model predictivity, efficient large-scale data integration methods such as rFASTCORMICS[1] allow the reconstruction of context-specific models relevant to diseases, patient groups, or individuals. Although these models can provide mechanistic insights into cellular behavior, the lack of standardized framework for model analysis still complicates their interpretation.

Here, we present an analysis pipeline for GSMMs, as well as an updated version of rFASTCORMICS for an integration of RNA-Seq data into GSMMs. This new version has been adapted for recent versions of MATLAB (2024b) and the Gurobi solver[2]. It addresses common constraints in context-specific GSMM reconstruction by allowing explicit incorporation of growth media but also their completion when insufficient. Alongside the expanded output provided throughout the reconstruction process, as integrated core and uptake reactions, we developed an analysis pipeline offering a documented, reproducible, and consistent workflow for GSMM analysis, with the aim of supporting follow-up across models and projects within the metabolic-modelling community. Although the pipeline was designed to analyze context-specific models generated with rFASTCORMICS, it remains applicable to any COBRA-format GSMM.

The pipeline is divided into three main steps: model reconstruction and project initialization, single-model analysis, and model comparison. The pipeline can be applied to a single model or, more interestingly, to multiple models representing different conditions, and it generates reports summarizing results and figures. It integrates well-established methods such as Flux Balance Analysis, gene deletion, and sampling, while also performing an exploratory analysis of the high-dimensional output generated. By identifying limiting reactions, differentially expressed pathways, metabolite turnover, and essential genes in a given context, it guides users toward the metabolic pathways and individual reactions of interest. The pipeline is under continuous development, supporting regular updating, and aims to progressively incorporate additional methods and approaches such as IDARE2 visualizations[3], to provide insights into mechanistic shifts and metabolic flow reorganization.

Overall, our pipeline fills the current gap of standardized workflow for GSMM analysis, and facilitates the extraction of robust and biologically meaningful insights from context-specific models.

1. Pacheco, M.P. et al. (2019). Identifying and targeting cancer-specific metabolism with network-based drug target prediction. *EBioMedicine*, 43, 98–106.
2. Gurobi Optimization, LLC (2024). Gurobi Optimizer Reference Manual.
3. Pfau, T., Galhardo, M., Lin, J., & Sauter, T. (2021). IDARE2: simultaneous visualisation of multiomics data in Cytoscape. *Metabolites*, 11(5), 300.

Keywords: Metabolic modeling, RNAseq integration, Context-specific model, Analysis pipeline, Standardized framework

O36

scFASTCORMICS 2.0: Fast and Scalable Context-Specific Metabolic Modeling from Single-Cell RNA-seq Data of the Tumor Microenvironment

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Oral presentation

Metabolic heterogeneity within the tumor microenvironment (TME) plays a pivotal role in immune evasion and therapy resistance, yet it remains poorly characterized at single-cell resolution. Single-cell profiling techniques offer unprecedented insights into cellular heterogeneity, which arises from nutrients and oxygen gradients, but they generate massive datasets that complicate data analysis and knowledge extraction. In 2022, we published scFASTCORMICS (Pacheco et al., 2022), a network contextualization algorithm that builds multi-cell population genome-scale models from single-cell RNA-seq data. These multicell models contain subnetworks that capture the signatures of the metabolic variations between cellular clusters, allowing us to predict metabolic exchanges between clusters. scFASTCORMICS was also used to study the impact of the MIRO1 mutation in the context of Parkinson’s disease-associated dopaminergic neuron loss (Zagare et al., 2025). Recently, the size of datasets, in terms of the number of cells and patients, has increased exponentially, which called for a new version of scFASTCORMICS with lower computational demands in terms of time and resources: scFASTCORMICS 2.0. It includes updated FASTCC and FASTCORE for large networks and improves robustness using complete expression profiles. This new version can be run on a standard laptop (with 4 cores and 16 GB of RAM) with a larger number of cells, and it is 16 times faster than the previous version. As an example, scFASTCORMICS 2.0 reconstructs a multi-cell model from 64,000 cells across 127 patients in under 20 minutes without optimization, and in 6 hours with the tuning step. The improvement in efficiency allows users without access to high-performance computing to build multi-cell population models from large single-cell RNA-seq datasets on their laptops and run analyses of high computational demands, like cross-validation and full parameter optimization, with potential use in microbiome reconstruction and spatial metabolic modeling. Preliminary results on CRC datasets showed that scFASTCORMICS captures metabolic variations consistent with the cellular annotations identified by Seurat. Pathway analysis revealed the activation of biosynthetic pathways, amino acid metabolism, and redox maintenance pathways in CRC epithelial clusters, reflecting metabolic rewiring associated with the Warburg effect. The models predicted metabolite exchanges, between tumor and immune populations, like glucose and lactate competition in the TME, supporting their potential to study metabolism-driven immune suppression and cancer–immune crosstalk. We are currently applying scFASTCORMICS 2.0 to identify key metabolites involved in cancer–immune crosstalk and evaluating the metabolic plasticity of immune and stromal cells within the colorectal cancer TME. We are particularly interested in testing how targeted nutrient interventions, guided by predicted metabolic vulnerabilities, could shift the TME from tumor-promoting to a tumor-restrictive state. By addressing key computational and biological challenges, this work enables deeper investigation into metabolism-driven immune suppression and opens new avenues for rational, subtype-specific therapeutic strategies across heterogeneous tumor ecosystems.

Keywords: metabolic heterogeneity , tumor microenvironment, network contextualization , single-cell resolution, Pathway analysis

O37

Functional tracer proteo-metabolomics: a toolbox to study cellular metabolism and protein modification dynamics

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Oral presentation

Cellular homeostasis emerges from the dynamic coordination of metabolic and signalling networks, with protein modifications acting as key regulatory interfaces. Central metabolites, such as acetyl-coenzyme A (acetyl-CoA) and S-Adenosyl-L-methionine (SAM), occupy a pivotal role in this integration by functioning both as metabolic intermediates and as direct donors for protein modifications. Perturbations in these interconnected layers of control are increasingly recognised as fundamental drivers of disease,

including cancer and metabolic disorders. Our research aims to unravel the mechanistic basis of this crosstalk through the development of innovative cross-OMICs (X-OMICs) strategies that integrate proteomics, metabolomics, and fluxomics with computational modelling. By combining these complementary approaches, we seek to quantitatively map the dynamic interplay between metabolic states and protein modification landscapes, thereby establishing a systems-level framework for understanding cellular regulation. To achieve metabolite-resolved insights into metabolic dynamics, we have developed a mass spectrometric metabolic phenotyper (M3P). This multiplexed tracer metabolomics platform combines stable isotope-labelled tracers (glucose & glutamine) with a rapid mass spectrometry workflow to quantify flux through central pathways, including glycolysis, the TCA cycle, and glutaminolysis. M3P enables robust and scalable metabolic phenotyping across diverse biological systems, providing pathway-resolved insights into metabolic reprogramming and revealing specific metabolic responses to perturbations such as kinase inhibition. In addition, we introduce tracer proteo-metabolomics, an integrated X-OMICs approach that simultaneously captures metabolite turnover (e.g. acetyl-CoA, S-adenosylmethionine) and protein modification dynamics (e.g. acetylation, methylation). This framework allows us to disentangle metabolic from epigenetic contributions to cellular regulation. We are currently applying these approaches to investigate how environmental stressors, including arsenite and bisphenol, and histone deacetylase inhibition reshape metabolic and epigenetic landscapes.

Keywords: tracer proteo-metabolomics, mass spectrometry, protein modification

O38

Developing Approaches for Knowledge-Driven Protein 3D Structure Prediction: Next Steps Beyond AI

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Oral presentation

As deep learning approaches such as AlphaFold continue to redefine structural biology, their limitations highlight persistent challenges, including high computational demands, dependence on homologous structural data, limited interpretability, difficulty with orphan, membrane, multistate and disordered proteins, and insufficient sensitivity to mutation-driven structural changes. By contrast, we take a knowledge-driven approach to protein 3D structure and function prediction based on genetic and biophysical principles of amino acid residue pairing (the proteomic code), rotameric/geometric shapes, and relay information system (RIS) mechanisms which represent interpretable fundamentals for protein 3D structure and function prediction methodologies accessing constraint-driven simulation protocols. Further knowledge gained by our approach and the broad scope of protein families accessible to our approach should also benefit future AI strategies.

Keywords: Protein folding, Molecular dynamics, Protein structure prediction, Knowledge-driven, Proteomic code

Systems biology communities & services

Chaired by: Carissa Bleker

The ELIXIR Systems Biology Community and Advancing FAIR and Trustworthy Systems Biology: From Principles to AI-Enhanced Practice

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Oral presentation

Despite the growing importance of mathematical modelling in biology, many published models remain difficult to reproduce, reuse, or integrate, limiting their scientific impact. The ELIXIR Systems Biology Community, founded in 2022, has worked to address this by synthesising FAIR (Findable, Accessible, Interoperable, Reusable) and CURE (Credible, Understandable, Reproducible, Extensible) principles into actionable guidance for the community. Through the SYBEL project, we mapped connections between researchers and essential tools and data resources, demonstrating that access mechanisms are as vital as the resources themselves for enabling reproducible research. Drawing on published recommendations, assessment frameworks, and community use cases, we identified substantial consensus around findability, accessibility, and interoperability for systems biology models, while reusability definitions and operational practices remain heterogeneous. We propose ten practical recommendations centred on seven key considerations during model development: designing interpretable models; verifying and validating them; using standards to increase interoperability; ensuring reproducible simulation results; depositing models and associated code in persistent repositories; and providing thorough model description and usage guidance. In parallel, we have developed curated FAIRsharing collections documenting standards and databases, bio.tools collections cataloguing essential software, and are developing an RDMKit page providing practical implementation guidance — all directly leveraging ELIXIR Recommended Interoperability Resources and Core Data Resources. Looking forward, we are exploring how artificial intelligence and knowledge graphs can transform systems biology workflows: AI-assisted curation can accelerate model and dataset annotation, while knowledge graphs enhance integration across heterogeneous data sources. For modelling workflows specifically, AI tools can ease access to

datasets, suggest appropriate formalisms, validate model structure, and propose mechanistic hypotheses grounded in literature. AI-enabled data-driven models also provide a synergistic complement to knowledge-based mechanistic models. By combining robust data management practices with emerging AI capabilities the Community aims to reduce barriers in systems biology research and accelerate discovery while maintaining the rigour essential for reproducibility.

Keywords: FAIR, CURE, Standards

O40

Improving Accessibility, Curation and Reusability of Enzyme Kinetic Data in SABIO-RK

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Oral presentation

SABIO-RK (<https://sabiork.h-its.org>) is a manually curated database providing comprehensive information on biochemical reaction kinetics for systems biology, computational modeling, and enzymology research. For more than 20 years, SABIO-RK has served as a central resource for experimentally measured enzyme kinetic data required for the simulation and quantitative analysis of complex biochemical networks. Each database entry is centered on a biochemical reaction and contains detailed information on kinetic parameters, rate equations, kinetic laws, experimental conditions, reactants, enzymes, and biological origin. To address increasing demands for usability and scalability, SABIO-RK has undergone a comprehensive redesign of both its technical infrastructure and user interface. The updated system integrates data input, curation, and public access into a unified framework based on a JSON-based data model. Full version control and change tracking have been implemented to improve transparency and reproducibility. The new web interface provides a more streamlined, intuitive, and efficient user experience. Improved navigation, enhanced search and filtering capabilities, and a modernized design facilitate easier exploration and analysis of biochemical reaction data. The new Browse functionality offers a structured overview of database contents, while the Results Explorer enables interactive refinement and comparison of search results. Search queries can now be saved and reused, and results can be exported in different formats for downstream computational analysis and model integration. Powerful and secure RESTful API with full version control has been implemented to access SABIO-RK data programmatically e.g., for integration into other applications and workflows. The new SABIO-RK also introduces major improvements to the curation workflow and enhanced curator assistance and supports user feedback and future community curation workflows.

Keywords: Database, Biochemical Reaction Kinetics, Enzyme Kinetics, Systems Biology, Modelling

O41

Interfacing systems biology diagrams and Large Language Models with the MINERVA Platform

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Oral presentation

Molecular interaction diagrams allow to encode domain knowledge of physiology and pathology into systems biology formats allowing their computational use. These diagrams are developed to support systems-level research in a specific area, including diseases or complex physiological processes. Development and use of such diagrams require a dedicated toolset for online browsing, data overlay, content management and programmatic endpoints. Importantly, integration of Large Language Models (LLMs) offers a number of advantages when building and analysing such systems biology oriented resources.

The MINERVA Platform is a software supporting visualisation of molecular interaction diagrams, focused on their exploration, visual data analytics, and interoperability of systems biology formats. MINERVA enables setup of a dedicated web-services supporting content created using dedicated editors like

CellDesigner or Newt, their online interactive display, annotation, management, and integration with omics data. Importantly, MINERVA has been evolving since over a decade, and its roadmap is aligned with the feedback of a broad user community. Recent implementation of Machine Context Protocol in MINERVA facilitates LLM integration, leading to streamlined content management and exploration.

We will present key features of the MINERVA Platform, including support of systems biology standards, dedicated API and content sharing via a common registry. LLM use supported by the dedicated MCP will be demonstrated using a large-scale COVID-19 Disease Map resource. We will conclude by discussing productivity of LLM support for a range of tasks related to systems biology diagrams.

Keywords: disease maps, Large Language Models, systems biomedicine

Theory and dynamics of metabolic modelling (Part 3)

Chaired by: Stefan Schuster

O42

Oscillatory wave propagation in yeast and β -cell populations

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Oral presentation

Metabolic oscillations are widespread in biology, and whereas their function at single cell level is not always clear, for intercellular communication and synchronisation, a repetitive dynamic signal is essential, e.g. heart cell coupling. In healthy individuals, insulin is secreted in pulses and a loss of pulsatility is an early hallmark of diabetes. Emerging evidence suggests glycolytic oscillations in β -cells drive pulsatile insulin secretion. In order to produce oscillatory insulin concentrations in the blood, β -cells in the pancreas must be synchronised - a remarkable feat, given the heterogeneity in millions of islets of Langerhans in the organ.

Synchronisation of weakly coupled oscillators has been well-studied in the model organism *Saccharomyces cerevisiae*, for which detailed mechanistic models simulate the system well. In order to study synchronisation, one must be able to follow individual cell dynamics. We developed fluorescent probes for yeast and β -cells and followed oscillatory wave propagation through populations of cells.

We propose that metabolic hubs of sufficiently high biomass concentration can function as initiators of oscillatory waves in β -cells. The hypothesis is tested experimentally in micro-fluidic chambers and analysed with detailed mechanistic models for yeast, and core models for β -cells.

Cells in initiator hubs might be connected via gap-junctions and synchronise via electrochemical signalling, but longer distance communication must occur via extracellular communication. A higher order structure might coordinate individual hubs in the pancreas, leading to synchronised oscillations at the tissue level.

Keywords: metabolic oscillations, synchronisation, insulin production, wave propagation, mathematical modelling

O43

Quantitative Phasor Analysis of Biological Oscillators

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Oral presentation

Sustained limit-cycle oscillations in metabolite concentrations and reaction rates characterise many biochemical networks. Traditional analytical methods like phase plane diagrams and polar phase plane plots struggle to scale with system dimensionality or capture a complete mechanistic view of network regulation. To address this, we adapted phasor representations, a technique from electrical engineering, to quantify and compare biological oscillators across models and experimental data.

In phasor analysis, periodic time-domain signals are transformed into the frequency domain via Fourier transforms, yielding phasors that represent the oscillating signals' peak amplitudes and phase angles. By incorporating both metabolite concentrations and reaction rates, this approach provides a unified view of how oscillations are transduced or absorbed across reaction chains. It handles sinusoidal and non-sinusoidal signals and is unrestricted by the dimensional limits of phase plane methods. We implemented the framework as a reusable software package in Wolfram Mathematica.

We applied the analysis to the yeast glycolytic pathway using multiple kinetic models of varying dimensionality and experimental datasets from intact cells and cell extracts. Results revealed a conserved oscillatory mechanism and quantitative similarities across models and datasets not apparent from standard dynamical analyses. Phosphofructokinase (PFK) emerged consistently as an important driver and destabiliser of oscillations in glycolytic intermediates and ATP across models and datasets, despite marked qualitative differences between them. Novel "drive-destabilise" and "drive-damp" diagrams further enabled quantification of how metabolites, particularly the adenylates acting through PFK, affect oscillatory behaviour, yielding mechanistic insights not evident from rate equations alone.

Phasor analysis connects individual reaction kinetics to emergent system-wide oscillations, offering a scalable tool to validate kinetic models and reveal the regulatory mechanisms underlying biological rhythms.

Keywords: Phasor Analysis, Biological Oscillators, Glycolysis

O44

Age-based approach to characterize the dynamics of cellular processes

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Oral presentation

Cells continuously produce and degrade molecules, essential for maintaining homeostasis. The study of these dynamics has gained momentum since the development of pulse-chase methods, utilizing fluorescent or isotopic labeling to assess properties such as turnover rates or half-lives. However, standard analyses of these experiments often depend on assumptions such as the homogeneity of analyzed molecules or their immediate labeling, which do not always hold. We show that the readouts of steady-state dynamic labeling experiments can be interpreted as the distribution of metabolic ages, defined as the time since each molecule entered the metabolic system, and that metabolic ages can be quantified with minimal assumptions. Using this age-based interpretation, we demonstrate how the experimentally observed labeling dynamics is connected to a variety of dynamic parameters including half-lives, decay rates, and residence times and how these interpretations are affected by the conditions of delayed input, cell growth, or complex degradation patterns. To aid in the experimental quantification of dynamic parameters, we introduce a compartmental model framework as well as an open-source software package. We illustrate the framework's practical utility by quantifying dynamic parameters and determining the

kinetic pool structure of budding yeast proteins at optimal and sub-optimal growth temperatures.

Keywords: isotopic labeling, compartmental model, metabolic age, residence time

O45

Clostridial acidogenesis product profiles are discontinuous: a thermodynamic hypothesis

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Oral presentation

At neutral pH, Clostridial fermentative catabolism is typically acidogenic, with a product profile dominated by acetate and butyrate. In this pathway, H₂ acts as a terminal electron acceptor via hydrogenases, which increases ATP-producing potential from glucose. Acetate production is characterised by both higher ATP and higher H₂ yields, rendering it more desirable but also more thermodynamically limited by H₂ accumulation. It is commonly understood that Clostridia can adjust the ratio of acetate to butyrate (Ace:But) produced to maximise ATP while maintaining sufficient pathway driving forces to sustain a high flux. The feasibility of the pathways underlying these product ratios are seldom explicitly investigated, however.

First, we decompose a Clostridial catabolic network into elementary flux modes (EFMs) that represent three product profiles: Homoacetic (acetate only), Equimolar (equal molar amounts of acetate and butyrate), and Homobutyric (butyrate only). These represent Ace:But ratios of 1:0, 1:1, and 0:1, respectively. Ratios intermediate to these can only occur by combining (blending) EFMs.

We then implement the well-known maximum-minimum driving force (MDF) analysis to test the thermodynamic favourability of the pathways underlying a spectrum of Ace:But ratios, including EFMs and blended EFMs. MDF is an optimiser which finds metabolite concentrations that yield the highest minimum DF. The implication is that reactions with lower DFs are less efficient and require higher enzyme levels to reach a similar net forward flux.

We find that blended EFMs are less thermodynamically efficient than their constituent EFMs. This is due to the co-occurrence of different hydrogenases with different optimal ratios of redox carriers. As two different redox ratios cannot be maintained, one hydrogenase inevitable has very high DF, which decreases the DF available for the reactions. This leads to a substantially lower minimum DF and a higher enzyme cost for operating blended EFMs.

These thermodynamic constraints imply that Clostridia growing on glucose-limited media exhibit relatively fixed Ace:But ratios with low sensitivity to H₂. This contradicts the common assumption that the Ace:But ratio represents a continuum of ATP-maximising possibilities. Literature data is also re-analysed to show that, indeed, especially fast-growing anaerobes – often dominated by Clostridia spp. – are not reported to change their Ace:But product ratio in response to changes in the pH₂. Slower-growing cultures, however, are more responsive to pH₂, suggesting that proteome constraints might play a role in the flexibility of Clostridia to alter their Ace:But ratio. This work deepens our understanding of the mechanisms behind the observed product profiles in Clostridia and in anaerobes more generally.

Keywords: anaerobic fermentation, Clostridia, thermodynamics, maximum-minimum driving force

O46

Making sense of time series with universal differential equations

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Oral presentation

Mechanistic models based on ordinary differential equations (ODEs) are a cornerstone of systems biology, but their predictive power is limited by our ability to specify every model term a priori. When biological mechanisms are partially unknown or too complex to parameterize from first principles, the gap between model and data grows, and classical fitting approaches cannot close it.

Universal differential equations (UDEs) offer a principled way to bridge this gap. A UDE replaces unknown or uncertain model terms with trainable function approximators, typically neural networks, embedded directly within an ODE system. The mechanistic scaffold is preserved, the unknown parts are learned from time series data, and the result remains interpretable in biological terms.

We demonstrate this approach across two use cases from plant systems biology.

First, in a model of sugar metabolism, we show that UDEs recover intracellular metabolic fluxes directly from concentration time series, without requiring explicit rate laws. The learned flux functions reproduce known regulatory features and generalize across experimental perturbations, providing a data-driven complement to traditional kinetic modeling.

Second, we apply UDEs to the identification of parameters governing pulse amplitude modulation (PAM) fluorometry protocols. PAM measurements are widely used to characterize photosynthetic state, but the relationship between instrument protocol and observed signal depends on parameters that are difficult to determine independently. By embedding the unknown protocol response as a learnable term within a mechanistic photosynthesis model, we recover these parameters directly from experimental fluorescence traces.

Together, these examples illustrate a general workflow: start with a mechanistic ODE model, identify the poorly constrained terms, replace them with neural network surrogates, and train on time series data. The result retains the interpretability of a mechanistic model while gaining the flexibility to learn where prior knowledge is insufficient.

UDEs represent a practical entry point into hybrid modeling for systems biologists already working with ODE-based models and time series data.

Keywords: universal differential equations, hybrid modeling, time series, photosynthesis

O47

FASTERCC: Accelerating Flux Consistency Testing and Context-Specific Reconstruction for Large-Scale Metabolic Network Models

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Oral presentation

The increase in size of metabolic network models especially with the advent of single-cell data calls for scalable reconstruction and analysis tools. Such models, often used for drug discovery and the analysis of microbial communities rely on consistency testing and reconstruction algorithms such as FASTCORE and FASTCC. However, with models nowadays comprising hundreds of thousands of reactions, the running times of such algorithms increased from few minutes to hours or days even with high performance computing. Experiments that require multiple reconstructions, such as parameter tuning or cross-validation, are practically infeasible in very large networks. Here we extend FASTCC (Vlassis et al., 2014) into FASTERCC, a scalable algorithm that not only accelerates flux consistency testing but, through the correction of reversibility and orientation of reactions also speeds up FASTCORE (Vlassis et al., 2014), a central tool in metabolic modeling. FASTERCC leverages structural information for removing type I and II dead-ends, the orientation of reversible reactions and correcting the reversibility of reactions that are structurally incapable of carrying flux in both directions prior to any feasibility tests. These improvements reduce drastically the running time of FASTERCC by a median 20-fold speedup in comparison to FASTCC for networks with a larger number of block reactions. The model cleaning performed. FASTERCC also reduces the computational time of downstream analyses, notably of FASTCORE up to 50%. The preprocessing of FasterCC is expected to benefit other FASTCORE-based workflows, toolboxes, and pipelines FASTCORMICS (Pacheco et al., 2015b), rFASTCORMICS (Pacheco et al., 2019), scFASTCORMICS (Pacheco et al., 2022), Cobra toolbox (Heirendt et al., 2019), FastGapFill (Thiele et al., 2014), PSAMM (Steffensen et al., 2016), TROPPO (Cunha et al., 2023), COMO (Bessell et al., 2023), TRFBA-CORE (Jamialahmadi et al., 2019), ThermOptiCS (Kumar S & Bhatt, 2025) Finally, correcting reversibility using FASTERCC has the potential to reduce computational times of workflows such as flux variability analysis, which tests reversible reactions in the

forward and the backward direction. It could also benefit workflows that split reversible reactions in two irreversible ones by reducing reaction counts and the limiting loop formation between the forward and backward reactions causing the appearance of blocked reactions. FASTERCC thus provides a foundation for scalable metabolic modelling in the era of large and complex biological datasets.

Keywords: Flux consistency analysis, Network reconstruction, Flux variability analysis, Metabolic Modeling, Single-cell systems biology

Author Index

A

Adiels, Caroline — [O42](#)
Anton, Mihail — [O39](#)
Atanasoski, Radoslav — [O27](#)

B

B K, Manjunatha — [P12](#)
Bakker, Barbara — [O2](#), [O3](#), [O17](#)
Balaaur, Irina — [O39](#)
Bayoumi, Salma — [P16](#)
Beck, Ashley — [O19](#)
Bekiaris, Pavlos Stephanos — [O33](#)
Belekar, Madhuri — [O15](#)
Bergmann, Frank — [O39](#)
Berns, Coen — [O31](#)
Bischoff, Rainer — [O3](#)
Biswas, Raagini — [O42](#)
Blaha, Marcel — [P11](#)
Blank, Lars — [O7](#)
Bleker, Carissa — [O11](#), [O27](#), [O39](#), [P5](#), [P6](#)
Bongiovanni, Laura — [O3](#)
Bos, Trijnie — [O2](#)
Botman, Dennis — [O42](#)
Breinich, Julian — [P11](#)
Bruggeman, Frank — [O1](#), [O24](#)
Brul, Stanley — [O31](#)
Busschaert, Michiel — [O12](#)

C

Carlson, Ross — [O19](#), [P9](#)
Černigoj, Lana — [P19](#)
Chakraborty, Suman — [O25](#)
Chapman, Hester — [P1](#)
Chiappalupi, Linda — [P1](#)
Cisse, El Hadji Malick — [O14](#)
Collin, Thomas — [O39](#)
Colombié, Sophie — [P17](#)
Conesa Cegarra, Ana Victoria — [O4](#)
Cordes, Henrik — [O7](#)

Correa, Sandra — [O11](#)
Curk, Tomaž — [O27](#), [P5](#)

D

Daggez, Alper — [P26](#)
de Blaauw, Pim — [O2](#)
de Bruin, Alain — [O3](#)
De Landtsheer, Sébastien — [P16](#)
de Rooij, Max — [O10](#)
de Vries, Marcel — [O3](#)
Derks, Terry — [O2](#), [O3](#)
Dias, Oscar — [O39](#)
Dimitriew, Wassili — [O23](#)
Dolenc Grošelj, Leja — [P2](#)
Domínguez-Romero, Elena — [O39](#)
du Preez, Franco — [O43](#)
Du, Martina — [P9](#)
Dwivedi, Shalu — [O29](#)
Džeroski, Sašo — [P19](#)

E

Ebeling, Josha — [P4](#)
Ebenhöh, Oliver — [O20](#), [P1](#), [P21](#)
Egger-Hörschinger, Anna-Sophia — [O37](#)
Erdani Kreft, Mateja — [P19](#)
Escoffier, Hugues — [O5](#)
Eunen, Karen van — [O17](#)
Evelo, Chris — [O39](#)
Evers, Bernard — [O17](#)

F

Fink, Katja — [P6](#)
Flouris, Vasilis — [O24](#)
Fon Tacer, Klementina — [P20](#)
Frioux, Clémence — [O22](#)

G

Gerding, Albert — [O2](#), [O3](#), [O17](#)
Goelzer, Anne — [P17](#)
Gonzalez, Evelyn — [O36](#), [O47](#)

Gonzalez-Cabaleiro, Rebeca — O45
Goobes, Yuval — P3
Goris, Maaïke — O3
Griebler, Christian — O12
Grigaitis, Pranas — P11
Gross Valle, Candelas — O2
Gruden, Kristina — O11, O27, P6

H

Haak, Anette — O3
Haddad, Yazan — O38
Halevy, Itay — P3, P13, P23
Halling, Peter — O34
Halužan Vasle, Ana — O16, P2, P10, P20, P25
Hameduh, Tareq — O38
Hancock, John — O39
Harish, P S — P12
Hassan, Tanvir — O29
Havinga, Rick — O3
Heger, Zbynek — O38
Heggland, Anne Elin — P26
Heiland, Ines — O9, O26, O37
Heiner-Fokkema, Rebecca — O2
Heinze, Elena Katharina — O9
Henning, Rob H. — O3
Hohenegg, Alina — O37
Homan, Esther — O2
Horvat, Simon — P8
Hotze, Madlen — O37
Høyland, Lena Elise — O26
Hu, Xiaoming — O40

J

Jalving, Mathilde — O17
Janev, Aleksandar — P19
Joshi-Michoel, Anagha Madhusudan — O9
Jovčevska, Ivana — P19
Jozef, Barbara — O8

K

Kaneti, Maayan — P23
Kavatalkar, Vijendra — O15
Kert, Aleš — P5

Kettner, Carsten — O34
Kilian, Joshua — O43
Kipura, Tobias — O37
Kiyuna, Ligia Akemi — O3
Klamt, Steffen — O33
Kloosterhuis, Niels — O3
Kokondoska Grgič, Vesna — P19
Kolenc, Klara — O16
Kološa, Katja — P19
Korady, Denis — P8
Korn, Lukas — O32
Kos, Aljaž — P25
Koster, Mirjam H. — O3
Kreft, Tinkara — P2
Krishnamurthy, Kishore — O2
Kuepfer, Lars — O7
Kunej, Tanja — P8
Kurlovics, Janis — P24
Kutmon, Martina — O39
Kwiatkowski, Marcel — O37

L

Ladreyt, Chloé — P17
Lanišnik Rižner, Tea — P19
Lejal, Vanille — O35
Levatić, Jurica — P19
Li, Shijia — O31
Liedl, Anna — O26
Lusnicenko, Margarita — P24

M

Makkinje, Miriam — O2, O3, O17
Martines, Anne-Claire M. F. — O3
Martins dos Santos, Vitor — O39
Matuszyńska, Anna — O14, O29, O39, P4
Meeson, Kate — O18, P18
Mehwald, Nora — O37
Miller, Andrew D. — O38
Mirhakkak, Mohammad — O23
Moretti, Sebastien — O39
Mosimann, Sven Lukas — O8
Moškon, Miha — O16, P2, P8, P10, P15, P20, P25

Mraz, Miha — P2, P15
Muller, Coralie — O22
Müller, Wolfgang — O40, P26
Munsamy, Alison — O42

N

Nahtigal, Katarina — P2
Niarakis, Anna — O39
Nies, Tim — P7
Nikoloski, Zoran — O11
Noor, Elad — O44

O

O'Donovan, Shauna — O10
Odendaal, Christoff — O45
Oldiges, Marco — O7
Olinga, Peter — O2
Onischenko, Evgeny — O44
Oosterveer, Maaïke — O2
Oosterveer, Maaïke H. — O3
Ostaszewski, Marek — O39, O41

P

Panagiotou, Gianni — O23
Pastva, Samuel — O28
Pavlič, Renata — P19
Persitz, Ingrid — O24
Petek, Marko — O11
Petrovič, Filip — P20
Pires Pacheco, Maria — O35, O36, O47
Poolman, Mark — O21
Praček, Sergej — O27, P6
Prigent, Sylvain — O22
Prosenc Zmrzljak, Uršula — P8
Pušnik, Žiga — P22
Putnam, Campbell — O19

R

Raghunathan, Anu — O15
Ramirez Mazo, Carolina — O9
Rasool, Saad — P18
Reijngoud, Dirk-Jan — O3, O17
Remeijer, Maaïke — O24
Rey, Maja — O40, P26

Režen, Tadeja — P15
Röblitz, Susanna — O9
Rocha, Miguel — O39
Rohwer, Johann — O34
Rolle, Pablo — O13
Rozman, Damjana — P2, P15
Rutten, Martijn — O2

S

Safranek, David — O28, O39
Salinas-Te, Luis A. — O1
Sartison, Nick — O37
Satagopam, Venkata — O41
Sauter, Thomas — O5, O35, O36, O47, P16
Sayin, A. Zeynep — O7
Schagerl, Michael — O12
Schäuble, Sascha — O23
Schirmer, Kristin — O8
Schlüter, Flora — P21
Schneider, Reinhard — O41
Schuster, Stefan — O23, O25, O29, O32
Schwartz, Jean-Marc — O18, P18
Shan, Yangwei — O31
Shaw, Klarissa — O42, P14
Sheriff, Rahuman — O39
Simoneta, Špela — P8
Sinreih, Maša — P19
Skubic, Cene — P2, P15
Smijakova, Eva — O28
Smit, Marieke — O3
Snoep, Jacky — O1, O6, O42, O43, P14
Solano Gutierrez, Juan Sebastian — P20
Soons, Zita — O7
Stalidzans, Egils — P24
Stare, Katja — O11
Suarez-Diez, Maria — O39
Subramanian, Abhishek — P12
Summerton, Tasmin — O6
Šuštar, Klara — P5

T

Tavares, Rui — P24
Teusink, Bas — O1

Thomas, Leonie — [O35](#)

Thomma, Bart — [P21](#)

Tome, Miha — [O8](#)

Tutar, Zuhtu — [P18](#)

U

Umek, Nejc — [P8](#)

V

van Aalst, Marvin — [O46](#), [P7](#)

van de Sluis, Bart — [O2](#)

van Niekerk, Dawie — [O6](#), [O42](#), [O43](#), [P14](#)

van Riel, Natal — [O10](#)

van Wyk, Morne — [O42](#)

Verheijen, Marit — [O45](#)

Verma, Pareena — [O21](#)

Vermeire, Florence — [O12](#)

W

Walakira, Andrew — [P15](#)

Waldherr, Steffen — [O12](#), [O13](#)

Waltemath, Dagmar — [O39](#)

Westerhoff, Hans — [O34](#)

Wittig, Ulrike — [O39](#), [O40](#)

Wolters, Justina — [O2](#), [O3](#)

Wortel, Meike — [O31](#)

Y

Yerushalmi, Tamir — [P13](#)

Z

Zagorščak, Maja — [O11](#), [O27](#)

Zeljковиć, Ida — [O16](#)

Zeljковиć, Irma — [P8](#)

Zhang, Jianbo — [O31](#)

Zhang, Mingjia — [O17](#)

Zhang, Wenxuan — [O3](#)

Zhang, Yichi — [P11](#)

Ziegler, Mathias — [O26](#)

Zimmermann, Johannes — [O30](#)

Zrimec, Jan — [O11](#), [O39](#), [P5](#)

Županič, Anže — [O8](#), [O27](#), [O39](#), [P6](#)

Keyword Index

#

[13C metabolic flux analysis](#) — [O17](#)

[3D cell culture](#) — [P19](#)

A

[ACC](#) — [O13](#)

[Acute cold exposure](#) — [O3](#)

[adiabatic approximation](#) — [O25](#)

[advanced cellular models](#) — [P19](#)

[AlphaFold2 structural analysis](#) — [P13](#)

[amino acid flux](#) — [O6](#)

[anaerobic fermentation](#) — [O45](#)

[Analysis pipeline](#) — [O35](#)

[Antimicrobial Resistance](#) — [O21](#)

[Attention-based encoder-decoder](#) — [P22](#)

[Autocatalytic pathway](#) — [O1](#)

[autotroph -heterotroph microbial community](#) — [O29](#)

B

[bacterial growth](#) — [P7](#)

[Biochemical Reaction Kinetics](#) — [O40](#)

[Biological Oscillators](#) — [O43](#)

[biomarkers](#) — [P24](#)

[blood pressure](#) — [O9](#)

[Boolean networks](#) — [O28](#)

[browser-based interface for ODE models](#) — [O29](#)

[butyrate](#) — [O31](#)

C

[calcium](#) — [P6](#)

[cancer](#) — [P25](#)

[Cancer metabolism](#) — [O18](#)

[Carbon Isotope Fractionation](#) — [P3](#)

[cell biology](#) — [O19](#)

[cell geometry](#) — [O19](#)

[cellular economics](#) — [P9](#)

[chemical defence](#) — [O32](#)

[Circadian rhythms](#) — [P2](#)

[Clostridia](#) — [O45](#)

[COBRA toolbox](#) — [P23](#)

[Cocntext-specific genome-scale metabolic models](#) — [P20](#)

[community dynamics](#) — [O31](#)

[compartmental model](#) — [O44](#)

[Complex tissue architecture](#) — [P8](#)

[Computational framework](#) — [P8](#)

[consortia assembly](#) — [P9](#)

[Constraint-based analysis](#) — [P18](#)

[Constraint-based and kinetic models](#) — [O33](#)

[constraint-based modeling](#) — [O11](#)

[Constraint-based modelling](#) — [O18](#)

[Context-specific model](#) — [O35](#)

[cross-feeding](#) — [O31](#)

[crowded environments](#) — [P7](#)

[CURE](#) — [O39](#)

D

[data analysis](#) — [O4](#)

[Database](#) — [O40](#)

[day-night rhythm](#) — [O25](#)

[deep learning](#) — [P5](#)

[Dichloroacetate](#) — [O17](#)

[disease maps](#) — [O41](#)

[documentation](#) — [P26](#)

[drug metabolism](#) — [P1](#)

[drugs](#) — [O7](#)

[Dynamic INCA modeling](#) — [O17](#)

[dynamic modeling](#) — [O27](#)

[Dynamic modeling of biological systems](#) — [P22](#)

E

[ecological and evolutionary dynamic](#) — [O29](#)

[Ecotoxicology](#) — [O8](#)

[energy limitation](#) — [P13](#)

[Enzyme constraint](#) — [O5](#)

[Enzyme Kinetics](#) — [O32](#), [O40](#), [P3](#)

[enzyme kinetics adaptation](#) — [P13](#)

[epithelial-mesenchymal transition](#) — [P19](#)

[Escherichia coli](#) — [O33](#)

[external input](#) — [O25](#)

F

FAIR — [O39](#), [P26](#)

Fast task- driven integrative network inference for tissues algorithm — [P20](#)

FBA — [P23](#)

fibroblast growth factor receptor — [O28](#)

fleshy fruit — [P17](#)

flux balance analysis — [O13](#), [P12](#), [P18](#)

Flux consistency analysis — [O47](#)

flux sampling — [O15](#)

Flux variability analysis — [O47](#)

fungal pathogenicity — [O23](#)

G

Gaussian process regression — [O12](#)

GEM — [P25](#)

Gene Essentiality — [O21](#)

gene expression — [P5](#)

Gene Regulatory Network inference — [P22](#)

Gene Regulatory Networks — [P22](#)

Generalised cosinor model — [P2](#)

Genome scale modeling — [O24](#)

Genome-scale metabolic model — [P18](#)

genome-scale metabolic modeling — [O31](#), [P11](#), [P24](#)

genome-scale metabolic modelling — [O6](#), [O13](#), [O15](#), [O16](#)

genome-scale metabolic models — [P15](#)

genome-scale metabolic networks — [P12](#)

Gibbs free energy — [O34](#)

glioblastoma — [O15](#)

Glucose-6-phosphate metabolism — [O2](#)

Glutamate metabolism — [O33](#)

Glycogen storage disease type I — [O2](#)

Glycolysis — [O1](#), [O43](#)

Graph Neural Networks — [P22](#)

Green algae — [O12](#)

GRN — [P10](#)

growth-defence trade-offs — [O11](#)

gut microbiome — [O30](#)

H

haemoglobin degradation — [O6](#)

Heat Stress — [O14](#)

hepatotoxicity — [P1](#)

Heterogenous data — [O22](#)

homeostasis — [O1](#)

Human metabolism — [O5](#)

hybrid modeling — [O46](#)

Hybrid modelling — [O10](#), [O12](#)

hypertension — [O9](#)

Hypoglycemia — [O3](#)

Hypoxia — [P2](#)

I

Imaging-based spatial transcriptomics — [P8](#)

immunotherapy — [P25](#)

insulin production — [O42](#)

Insulin resistance — [P14](#)

interactions — [P5](#)

ionic strength — [O34](#)

Isotopes — [P23](#)

isotopic labeling — [O44](#)

J

Julia — [O5](#)

K

kinetics — [O27](#)

Knowledge network — [O8](#)

Knowledge-driven — [O38](#)

L

Large Language Models — [O41](#)

liver toxicity — [O7](#)

logical network model — [P16](#)

Long-read transcriptomics — [O4](#)

M

machine learning — [P24](#)

machine learning sequence classification — [P13](#)

MAGE-A3 protein — [P20](#)

malic enzymes — [O15](#)

MAPK signalling — [O28](#)

mass spectrometry — [O37](#)

mathematical modelling — [O42](#)

maximum-minimum driving force — [O45](#)

MCAD deficiency — [O3](#)
 mechanistic modeling — [P21](#)
 Melanoma metabolism — [O17](#)
 meta-omics — [P11](#)
 metabolic age — [O44](#)
 metabolic cofactors — [O26](#)
 metabolic engineering — [O24](#), [P12](#)
 metabolic flux analysis — [O7](#)
 metabolic heterogeneity — [O36](#)
 Metabolic interaction — [O29](#)
 Metabolic modeling — [O23](#), [O35](#), [O47](#)
 Metabolic modeling approaches — [O33](#)
 metabolic modelling — [O5](#), [O21](#), [O22](#), [P12](#), [P17](#), [P23](#)
 metabolic oscillations — [O42](#)
 metabolic potential — [O34](#)
 metabolism — [O20](#)
 Metabolomics — [O22](#)
 methanogenesis — [P13](#)
 microbial communities — [P11](#)
 microbial community dynamics — [P21](#)
 microbial consortia — [P9](#)
 Microbial ecology — [O22](#)
 microbial growth — [O20](#)
 microbial physiology — [O30](#)
 microbiome — [O23](#)
 Minimal cut sets — [O24](#)
 Mitochondrial fatty acid oxidation disorders — [O3](#)
 model extraction methods — [P15](#)
 model refinement — [O28](#)
 modeling — [P10](#)
 Modelling — [O40](#)
 modelling synthetic community — [O29](#)
 Modular response analysis — [P14](#)
 Molecular dynamics — [O38](#)
 multi-omics — [P24](#)
N
 NAD, CoA and FAD — [O26](#)
 network analysis — [O27](#)
 network contextualization — [O36](#)
 Network reconstruction — [O47](#)

networks — [P5](#)
 non-autonomous differential equation — [O25](#)

O

ODE model — [O32](#), [P4](#)
 ODE modeling — [O14](#)
 omics data integration — [P15](#)
 Ovarian cancer — [O18](#)

P

Paraburkholderia dioscraeae MSB3 — [O13](#)
 Pathway analysis — [O36](#)
 Pentose phosphate pathway — [O17](#)
 Personalised medicine — [O10](#)
 pH — [O34](#)
 Phasor Analysis — [O43](#)
 phenotype control — [O28](#)
 Photoprotection — [P4](#)
 Photosynthesis — [O46](#), [P4](#)
 plant immune system — [P6](#)
 plant immunity — [P21](#)
 Plant system biology — [P17](#)
 plant-herbivore interaction — [O25](#)
 plants — [O27](#), [P6](#)
 Plasmodium falciparum — [O6](#)
 Population balance models — [O12](#)
 Post-squalene cholesterol biosynthesis — [P2](#)
 potato metabolism — [O11](#)
 Precision-cut liver slices — [O2](#)
 probabilistic modeling — [P16](#)
 Proliferation — [O8](#)
 proliferation dynamics — [P19](#)
 Protein folding — [O38](#)
 protein modification — [O37](#)
 Protein structure prediction — [O38](#)
 Proteomic code — [O38](#)
 Proteomics — [O5](#), [O7](#)
 Proton-motive force — [P4](#)
 Provenance — [P26](#)
R
 rate vs. yield tradeoff — [O30](#)
 reservoir computing — [P10](#)

residence time — [O44](#)
Resource allocation problem — [O32](#)
Resource Balance Analysis — [P17](#)
RIBO-seq — [O8](#)
RNAseq — [O18](#)
RNAseq integration — [O35](#)
Rubisco — [P3](#)
rules of life — [O19](#)

S

Scientific machine learning — [O10](#)
scRNA-seq data — [O16](#)
scRNAseq — [P25](#)
sex differences — [O9](#)
software development — [O4](#)
Signal propagation — [O8](#)
signaling — [P16](#)
signalling — [P6](#)
single-cell resolution — [O36](#)
Single-cell systems biology — [O47](#)
Skeletal muscle — [P8](#), [P14](#)
software — [P7](#)
spatial modeling — [P7](#)
Spreadsheets — [P26](#)
SQANTIverse — [O4](#)
stable isotope labelling — [O26](#)
Stable-isotope based fluxomics — [O2](#)
Standardized framework — [O35](#)
Standards — [O39](#)
Steady state — [O32](#)
Stress Memory — [O14](#)
Sulfite reduction — [P23](#)
surface area : volume — [O19](#)
synchronisation — [O42](#)

synthetic ecology — [P9](#)
synthetic lethality — [O15](#)
system biology — [O11](#)
Systems biology — [O14](#), [O19](#), [O21](#), [O22](#), [O27](#),
[O40](#), [P6](#), [P9](#)
systems biomedicine — [O41](#)
systems medicine — [O3](#), [P1](#)

T

targeted metabolomics — [O6](#)
TCA cycle alterations — [O2](#)
temperature — [O34](#)
Theoretical systems biology — [O33](#)
thermodynamics — [O20](#), [O45](#)
time series — [O46](#)
Time-series metabolomics — [P2](#)
tissue organization — [P7](#)
tracer proteo-metabolomics — [O37](#)
transcriptomics — [O7](#), [O14](#), [P20](#)
Transformation — [P26](#)
Triosephosphate isomerase 1 — [O18](#)
tumor microenvironment — [O36](#), [P19](#)
tumour heterogeneity — [O16](#)
Type 2 Diabetes — [P14](#)

U

universal differential equations — [O46](#)

V

variational auto encoder — [P25](#)
visualization — [P12](#)

W

wave propagation — [O42](#)
women's health — [O9](#)