METABOLIC PATHWAY ANALYSIS

Systems (biology + medicine)

12TH - 16TH AUGUST 2019
RIGA, LATVIA

EVENTS.LU.LV/MPA2019

NATIONAL DEVELOPMENT PLAN 2020

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Content:

Introduction

The Metabolic Pathway Analysis 2019 held in the newly built Academic Centre for Life Sciences in Riga is the seventh conference in MPA series. The conference comes to Latvia at a time of celebration – it is the centenary of Latvia as an independent country and its national university - the University of Latvia.

Earlier MPA meetings have been held in Jena, Germany (2005), Leiden, Netherlands (2009), Chester, United Kingdom (2011), Oxford, United Kingdom (2013), Braga, Portugal (2015) and Bozeman, Montana, USA (2017). The meeting has a primary focus on metabolism and interconnected processes. Conference includes invited and selected talks, poster sessions, as well as tutorials.

The conference consists of 6 sessions:

1. Systems medicine
2. Fundamentals of metabolic network structure
3. Reconstituted systems and synthetic biology
4. Pathways of primary and secondary metabolism
5. Applied metabolic systems analysis and engineering
6. Methodology and mathematical algorithms and software

The scientific and organising committee

Chair: Egils Stalidzans (University of Latvia, Riga, Latvia)
Ross P. Carlson (Montana State University, Bozeman, USA)
Oliver Ebenhoeh (Henrich Heine University, Germany)
Sabine Peres (University of Paris-Sud Paris-Saclay, France)
Mark Poolman (Oxford Brookes University, United Kingdom)
Isabel Rocha (ITQB, NOVA University Lisbon, Portugal)
Herbert Sauro (University of Washington, Seattle, USA)
Stefan Schuster (Friedrich-Schiller-University Jena, Germany)
Hyun-Seob Song (Pacific Northwest National Laboratory, USA)
Zita Soons (Maastricht University, The Netherlands)
Cong Trinh (University of Tennessee, Knoxville, USA)

The local organising committee

Chair: Darta Maija Zake (University of Latvia, Riga, Latvia)
Elina Dace (University of Latvia, Riga, Latvia)
Janis Kurlovics (University of Latvia, Riga, Latvia)
Kristaps Berzins (University of Latvia, Riga, Latvia)
Santa Prikule (University of Latvia, Riga, Latvia)
Agris Pentjuss (University of Latvia, Riga, Latvia)
Katrina Daila Neiburga (University of Latvia, Riga, Latvia)
Zane Ozolina (University of Latvia, Riga, Latvia)
Liva Stalidzane (University of Latvia, Riga, Latvia)

Invited speakers

Dong-Yup Lee
Sungkyunkwan University, South Korea

Herbert Sauro
University of Washington, United States

John Wain
Quadram Institute Bioscience, United Kingdom

Athel Cornish-Bowden
French National Centre for Scientific Research, France

Uwe Sauer
ETH Zurich, Switzerland

Anne Siegel
Univ Rennes, Inria, CNRS, IRISA, France

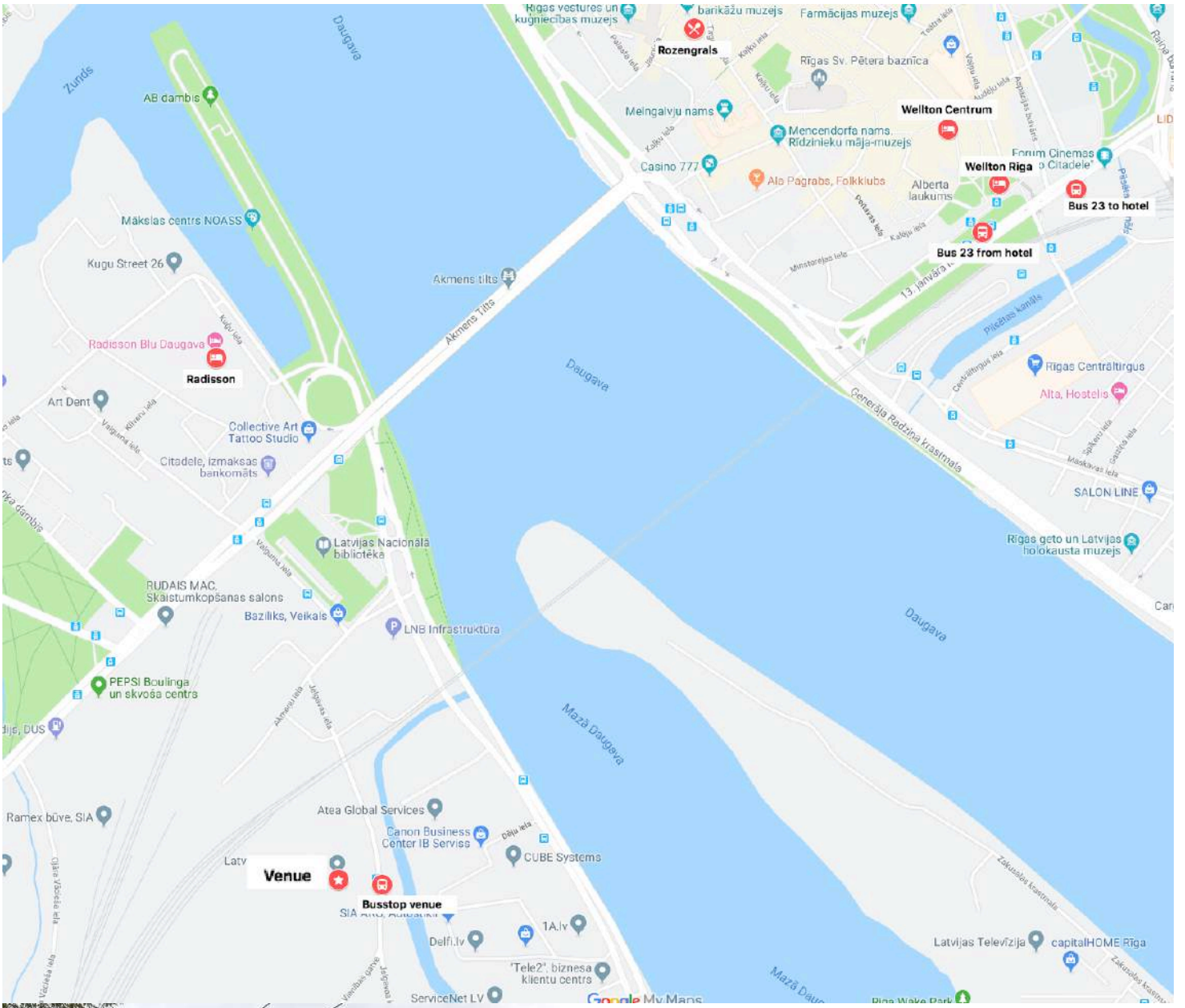
Adil Mardinoglu
KTH-Royal Institute of Technology, King's College London, Sweden and the United Kingdom

Harald H. H. W. Schmidt
Maastricht University, The Netherlands

Kathrin Thedieck
University of Innsbruck, Austria

Sponsors and contributors

We are thankful for the financial support from the European Regional Development Fund project Nr.1.1.1.5/18/I/016: The University of Latvia in the European Research Area – excellence, activity, mobility, capacity. As well as we acknowledge the US National Science Foundation for a student travel grant.



Use the QR code to add the conference map to your google maps
Alternatively: http://bit.do/MPA2019map

Venue

The event takes place in the University of Latvia Academic Center for Natural Sciences that was built in 2015 and currently holds the faculties of Biology, Chemistry, Geography and Medicine.

Venue address: Jelgavas street 1, Riga, Latvia

The conference oral presentations will happen on the 1st floor, auditorium 106 "Magnum".

The poster presentations will happen on the 2nd floor lobby.

Coffee breaks and lunch will be served in the 2nd floor courtyard.

The 1st day tutorials will happen on the 3rd floor - rooms 334, 335, 336.

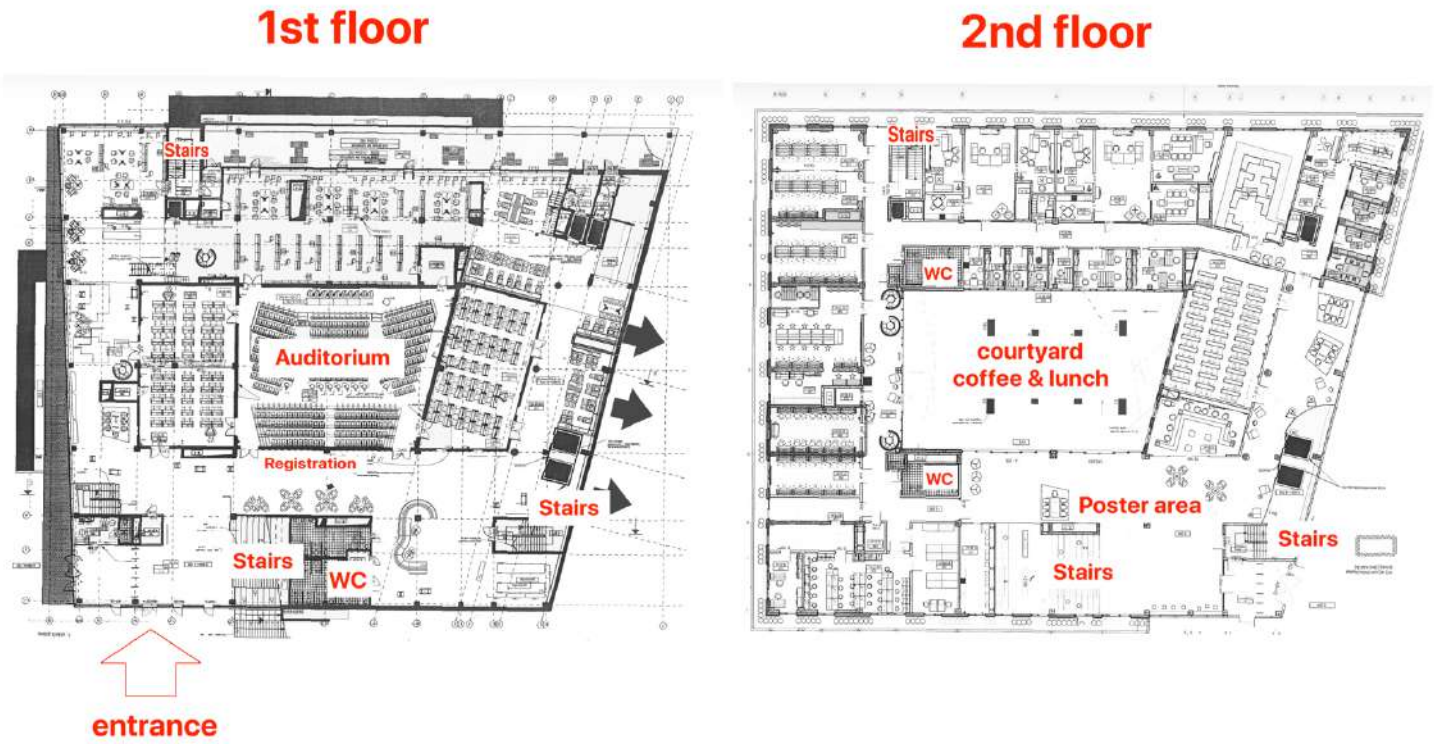
WIFI

Eduroam

LU-WIFI network

Username: wlan50

Password: metabolic



Accommodation

The participants will be staying at 3 different hotels, emails about your designated accommodation have been sent out.

If you have not received an email about your accommodation, please contact us at mpa2019@lu.lv immediately.

Accommodation No.1: Radisson Blu Daugava Hotel
Address: Kuģu street 24

Accommodation No.2: Wellton Riga Hotel & SPA
Address: Vaļņu street 49

Accommodation No.3: Wellton Centrum Hotel & SPA
Address: Kalēju street 49

Transport

There are two main ways of transport in the city - bus and taxi.

BUS: the best way to plan your trip and access timetables in English would be through the app https://www.trafi.com/ an alternative is to use the city's website https://saraksti.rigassatiksme.lv/index.html#riga/en.

To use the bus or other types of public transport you need a ticket called "e-talons" that costs 1,15EUR per ride if purchased at a kiosk and 2,00EUR if purchased at the driver. **Upon registration, you will receive a public transportation ticket that is valid for all modes of public transport for 5 days.**

Connections to the Airport: Bus No.22 is the only bus that connects the city to the airport. The bus stop is right outside the airport and the main stops in the city are
>the National Library "Nacionālā bibliotēka" - this is the closest stop to get to the conference venue and the Radisson Blu Daugava hotel
>the centre of the town "Autoosta" (or "13. Janvāra iela" if you are going to the airport), this is the closest stop to the hotels Wellton Riga and Wellton Centrum.
Bus schedule: https://saraksti.rigassatiksme.lv/index.html#bus/22/b-a/en

Connections to the conference venue: Bus No.23 takes you directly to the venue if you are leaving from the hotels Wellton Riga and Wellton Centrum, the right stop to get in is "13. Janvāra iela" and the stop to get out is the Academic Center "Latvijas Universitātes Akadēmiskais Centrs". If you are staying at the Radisson Blu Daugava Hotel, we suggest walking to the venue (~15 minutes) or taking a cab.
Bus schedule: https://saraksti.rigassatiksme.lv/index.html#bus/23/a-b/9114/en

TAXI: please be careful when ordering a taxi from the airport, find out the rate before you get in the car, otherwise there is a possibility that you will have to pay 50 euros to get to the centre of Riga.

There are however reliable taxi options:

1. Bolt (previously Taxify, functions just like Uber). To use it you need to install the app: https://bolt.eu/ It costs around 8EUR to get from the Airport to the centre of Riga.
   You can use the code 6MMLJ to get a 10EUR discount for your first ride.

2. Baltic Taxi. It is a company connected to the Airport and provides good service - they can be reached by calling the number +371 2008500 The rate is 2.13 EUR flat + 0.71 EUR/km and 0.14 EUR min.

Tutorials

On the first day of MPA we will be offering tutorials where you will be able to learn about the newest software in use and get advice from skilled professionals. Since the number of participants is limited for each tutorial, please only attend the tutorial that you have registered for. Tutorials will happen on the 3rd floor.

10:00 - 13:00 Tutorials 1

1.1. R334 "Modelling Dynamic Systems in Python" Oliver Ebenhöh

Description: The goal of the workshop is to teach students how dynamic systems based on ordinary differential equations can be simulated and analyzed with Python. Depending on the background, we will recapitulate some basic programming elements of the programming language Python and repeat some basics about differential equations. In the hands-on tutorial, we will use the well-documented Python package 'modelbase', which is designed to support the model construction and analysis process as a fully integrated part of the Python programming language. We will implement some simple systems, integrate these, and visualize the results for analysis. Participants are strongly encouraged to install Python and modelbase beforehand. Please see http://doi.org/10.5334/jors.236 and https://modelbase.readthedocs.io/en/latest/ on information on the modelbase software and the (simple) instructions on how to install.

1.2. R335 "Metabolic Modeling in the Department of Energy Systems Biology Knowledgebase (KBase)", José P. Faria, Janaka Edirisinghe

Description: The Department of Energy Systems Biology Knowledgebase (KBase; http://kbase.us) is a knowledge creation and discovery environment designed for both biologists and bioinformaticians. KBase integrates a variety of data and analysis tools, from DOE and other public services, into an easy-to-use platform that leverages scalable computing infrastructure to perform sophisticated systems biology analyses. KBase is freely available and a developer extensible platform enabling scientists to analyze their own data within the context of public data and share findings across the system. The Workshop will focus on the genome-scale modeling tools available in KBase. Participants will learn how to reconstruct and analyze metabolic models for microbes, plants, and communities.

1.3. R336 "Merlin - Software for Reconstruction of Genome-Scale Models", Isabel Rocha, Oscar Dias

14:00 - 17:30 Tutorials 2

2.1. R334 "Reproducibility and Standards in Metabolic Kinetic Modeling", Herbert Sauro

Description: The vast majority of published models in systems biology cannot be reproduced. In this tutorial, we will use Tellurium, a Python-based simulation environment that supports all current modeling standards. We will show users how to retrieve models from biomodels, turn such models into a readable form, simulate, change, then convert them back into SBML. The tutorial will also discuss other aspects of Tellurium including creating new models using the highly readable Antimony syntax, metabolic control analysis, bifurcation analysis, and parameter estimation. The tutorial will also demonstrate the new structural python package that can be used to compute conservation laws and elementary models. It is recommended that users download and install the software before the tutorial from tellurium.analogmachine.org. The software can run on Windows, Mac OS, and Linux.

2.2. R336 "Analyzing Metabolic Networks with CellNetAnalyzer", Axel von Kamp, Philipp Schneider, Steffen Klamt

Description: CellNetAnalyzer (CNA) is a MATLAB package for analyzing biological (metabolic, signalling and regulatory) networks and supports both command-line based operations, as well as a graphical user, interface with embedded network visualizations. In the first part of the tutorial (1,5h), we will demonstrate key features of CNA for stoichiometric and constraint-based modeling of metabolic networks (including flux (balance) analysis, flux, and yield optimization, elementary mode analysis, computational strain design with minimal cut sets and others). The second part of the tutorial (1,5h) will consist of hands-on exercises where the participants will learn how to use CellNetAnalyzer in practice.

Presentations

Oral presentations: The dimensions of the projection system at auditorium 106 is 16:9. The 3:4 prepared slides are displayed well keeping the proportion, but adding dark sidelines.
A computer for presentations will be provided. Please, provide your presentation on the USB memory.

If you are using your own laptop. Please prepare your laptop computer for the presentation and make a copy of your presentation on a USB stick. Analog (VGA, D-sub 15 pins) and digital (HDMI) connections are available. Please, check the connectivity and presentations before the talk. Sound will be available.

Time slot for general presentations is 20 minutes including questions and discussion.

If you have specific requests for your presentation, please write to mpa2019@lu.lv

Poster presentations: We recommend you to prepare your poster in the A0 portrait format. The poster board dimensions are 90,5 cm x 195,0 cm, portrait orientation.
Materials for fixation of the posters will be provided in the poster area.

Numbered boards will be available from Monday evening. The posters will be on display for the entire meeting. Presenters of odd/even-numbered posters are requested to attend their poster during the allocated session from 18:00 - 19:30 on Tuesday 13th of August (poster session I; odd numbers) and Thursday, 15th of August (poster session II; even numbers).

At the start of the poster session, there is an option to present poster Lightning talk about posters presented that day. Lightning talk duration is 60 seconds with one slide without questions afterward. That is kind of advertisement of your poster.

In case you want to present a Lightning talk about your poster, please, send one pdf slide (best would be in landscape) along with the name of the presenter of that slide to e-mail address mpa.lightningposters@gmail.com

That slide will be included in the presentation that will be created and operated by organizers during Lightning talk session.

The submission ends one day before the lightning talk. Slides that are sent later will be accepted if it will be possible.

Large format printing suggestion:

COPYPRO, Raina blvd. 17; working hours Mon-Sun 0:00-24:00
https://www.copypro.lv/en/print/large-format-printing

Contacts

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In any emergency situation you should call the free number 112
this is the contact number for the emergency services. This number can be used to contact police, fire brigade, ambulance, and gas emergency services. Operators can take calls in Latvian, Russian, English, and German.

SCHEDULE FOR METABOLIC PATHWAY ANALYSIS 2019
12.-16. August 2019, Riga, Latvia

			Monday, 12th of August	
From 08:00	1st floor		Registration	
10:00 - 17:30	3rd floor		Tutorials	
17:30 - 18:00			Coffee break	
18:00 - 18:45	Room 106	I1	Opening lecture: Harald H. H. W. Schmidt	The end of medicine as we know it
19:00 -21:00	2nd floor		Welcome reception	

			Tuesday, 13th of August	
From 08:30	1st floor		Registration	
09:00 - 09:20	Room 106		Opening of the conference	
	Room 106		Session 1.1 - Systems Medicine, Chair Egils Stalidzans	
09:20 - 09:55		I2	Invited speaker - Adil Mardinoglu	The use of systems biology in treatment of liver diseases
09:55 - 10:15		T1	Silvio Waschina, Johannes Zimmermann, Julia Pagel and Christoph Kaleta	Elucidating the metabolic processes within the gut microbiome that precede sepsis in preterm infants and remission in IBD patients
10:15 - 10:35		T2	Germán Andres Preciat Gonzalez, Luojiao Huang, Emma Schymanski, Thomas Hankemeier and Ronan Fleming	Atom mapping data for genome-scale metabolic network reconstructions; Application in human dopaminergic neuronal metabolism
10:35 - 11:00	2nd floor		Coffee break	
	Room 106		Session 1.2 - Systems Medicine, Chair Adil Mardinoglu	
11:00 -11:35		I3	Invited Speaker - Kathrin Thedieck	Systems approaches to metabolic signalling
11:35 - 11:55		T3	Jean-Marc Schwartz and Zita Soons	Fluxomics reveals cellular and molecular basis of increased renal ammoniagenesis
11:55 - 12:15		T4	Darta Zake, Egils Stalidzans, Linda Zaharenko and Janis Klovins	Physiologically based metformin pharmacokinetics model for estimation of therapeutic concentrations in various tissues
12:15 - 12:35		T5	Thomas Sauter, Tamara Bintener, Dominik Ternes, Dagmar Kulms, Serge Haan, Elisabeth Letellier and Maria Pires Pacheco	Identifying and targeting cancer-specific metabolism with network based drug target prediction
12:35 - 14:00	2nd floor		Lunch	
	Room 106		Session 2.1 Fundamentals of metabolic network structure, Chair Stefan Schuster	
14:00 - 14:35		I4	Inv. speaker - Athel Cornish - Bowden	Modern Theories of Life
14:35 - 14:55		T6	Stefan Mueller, Georg Regensburger and Juergen Zanghellini	Flux tope analysis: which combinations of reaction directions are (thermodynamically) feasible?
14:55 - 15:15		T7	José P. Faria, Filipe Liu, Janaka N. Edirisinghe, Samuel M.D. Seaver, James G. Jeffryes, Qizh Zhang, Pamela Weisenhorn, Boris Sadkhin, Nidhi Gupta, Tian Gu and Christopher S.	High Throughput Genome-Scale Metabolic Model Reconstruction and Reconciliation with Tn-seq Data
15:15 - 15:35	Room 106		Open MPA 2019 organising committee meeting	
15:35 - 16:00	2nd floor		Coffee break	
	Room 106		Session 2.2 Fundamentals of metabolic network structure, Chair Isabel Rocha	
16:00 - 16:20		T8	Tin Yau Pang and Martin Lercher	Natural selection on the extent of intracellular crowding
16:20 - 16:40		T9	John Barrett and Friedrich Srienc	Statistical Thermodynamics of Metabolic Reaction
16:40 - 17:00		T10	Filipe Liu, Samuel M.D. Seaver, José P. Faria, Janaka N. Edirisinghe, James G. Jeffryes, Tian Gu and Christopher S. Henry	Validation and Curation of Biochemical Networks through thermodynamics and visualization
17:00 - 17:20		T11	Nima Saadat and Ovidiu Popa	Impact of prophage encoded enzymes on the metabolic capacity of the hosts.
17:45 - 19:30	2nd floor		Poster session beginning with Lightning poster talks	

			Wednesday, 14th of August	
	Room 106		Session 3.1 Reconstituated Systems and Synthetc Biology, Chair Cong Trinh	
09:00 - 09:35		I5	Invited speaker - Herbert Sauro	A Menagerie of Systems Biology Standards With a Special Focus on the Synthetic Biology Open Language
09:35 - 09:55		T12	Ashley Beck, Tomas Gedeon, Jeffrey Heys and Ross Carlson	Surface area is a cellular resource that can be used to predict and design competitive biological organization
09:55 - 10:15		T13	Marian Breuer, Tyler Earnest, Chuck Merryman, Kim Wise, Lijie Sun, Michaela Lynott, Clyde A. Hutchison Iii, Hamilton Smith, John Lapek, David Gonzalez, Valerie De Crecy-Lagard, Drago Haas, Andrew D. Hanson, Piyush Labhsetwar, John Glass and Zaida Luthey-Schulten	Essential metabolism for a minimal cell
10:15 - 10:35		T14	Mikk Õun, Nikita Rom, Raivo Vilu, Vassili Kiritsenko, Kristo Abner, Taivo Lints and Maria Bubina	A Novel Tool for Metabolic Model Optimisation and Result Visualisation
10:35 - 11:00	2nd floor		Coffee break	
	Room 106		Session 3.2 Applied metabolic systems analysis ad engineering, Chair Kathrin Thedieck	
11:00 -11:35		I6	Invited speaker - John Wain	Changing Culture in Microbiology
11:35 - 11:55		T15	Steffen Klamt, Simon Boecker and Ahmed Zahoor	Extending the Scope of Enforced ATP Wasting as a Tool for Metabolic Engineering in Escherichia coli
11:55 - 12:15		T16	Debolina Sarkar and Costas Maranas	SNPeffect: Identifying Functional Roles of SNPs using Metabolic Network Information
12:15 - 12:35		T17	Stefan Schuster, Maximilian Fichtner and Severin Sasso	How to cope with the combinatorial complexity of fatty acids?
12:35 - 13:00			Collection of lunch packages	
13:00 - 19:00			Field trip	

			Thursday, 15th of August	
	Room 106		Session 4.1 Pathways of primary and secondary metabolism, Chair Hyun-Seob Song	
09:00 - 09:35		I7	Invited speaker - Uwe Sauer	Metabolic Coordination Through Metabolite-Protein Interactions
09:35 - 09:55		T18	Esther M. Sundermann, Martin J. Lercher and David Heckmann	In silico exploration of paths toward C4 metabolism
09:55 - 10:15		T19	Leonor Guedes Da Silva, Sergio Tomás Martínez, Mark C. M. van Loosdrecht and Aljoscha Wahl	The environment selects: Modeling intracellular energy allocation in microbial communities under dynamic environments
10:15 - 10:35		T20	Fernando Cruz, Catarina Ribeiro, Miguel Silva, Isabel Rocha, Ahmad A. Zeidan and Oscar Dias	What Can Multiple Genome-Scale Metabolic Models Unveil About the Same Organism? A Case Study of the Dairy Bacterium Streptococcus thermophilus
10:35 - 11:00	2nd floor		Coffee break	
	Room 106		Session 4.2 Pathways of primary and secondary metabolism, Chair Sabine Peres	
11:00 -11:35		T21	Jorgelindo da Veiga Moreira, Laurent Schwartz and Sabine Peres	Modulating mitochondria horsepower for biotechnological applications
11:35 - 11:55		T22	Martin H. Rau, Paula Gaspar, Maiken L. Jensen and Ahmad A. Zeidan	Genome-scale metabolic modeling of Streptococcus thermophilus uncovers the signature of milk adaptation
11:55 - 12:15		T23	Ross Carlson, Michael Henson, Luke Hanley and Matthew Fields	In silico and Multi-omics analysis of Reverse Diauxie in Pseudomonas aeruginosa
12:15 - 12:35		T24	Jürgen Zanghellini and Bianca Buchner	Comprehensive elementary mode analysis of Mycoplasma mycoides JCVI-syn3.0.
12:35 - 14:00	2nd floor		Lunch	
	Room 106		Session 5.1 Applied metabolic systems analysis ad engineering, Chair Herbert Sauro	
14:00 - 14:35		I8	Invited speaker - Dong-Yup Lee	Model-guided design and engineering of probiotic LAB system with host and microbiome interactions

14:35 - 14:55		T25	Egils Stalidzans, Agris Pentjuss and Atis Elsts	Automation of constrained kinetic metabolic model optimization by COPASI wrapper SpaceScanner
14:55 - 15:15		T26	Philipp Schneider and Steffen Klamt	Characterizing and Ranking Computed Metabolic Engineering Strategies
15:15 - 15:35		T27	Hyun-Seob Song, William Nelson, Joon-Yong Lee, Christopher Henry, Janaka Edirisinghe, Filipe Liu, James Stegen, Emily Graham, Kelly Wrighton, Kewei Chen, Xuehang Song, Jianqiu Zheng, Glenn Hammond, David Moulton, Xingyuan Chen and Tim Scheibe	Multiomics-based Metabolic Network Reconstruction and Pathway Analysis for Predictive Biogeochemical Modeling
15:35 - 16:00	2nd floor		Coffee break	
	Room 106		Session 5.2 Applied metabolic systems analysis and engineering, Chair Dong-Yup Lee	
16:00 - 16:20		T28	Katharina Nöh and Axel Theorell	A Critical View on Ockham's Razor as Criterion for Model Selection in Systems Biology
16:20 - 16:40		T29	Oliver Hädicke	In silico profiling of Escherichia coli and Saccharomyces cerevisiae as cannabinoid factories.
16:40 - 17:00		T30	Sean Mack, Eric Hill, Young-Mo Kim, Lye-Meng Markillie, Teresa Palazzo, Karl Weitz, Robert Young, Ganesh Sriram and Daniel Dwyer	Integrated Flux Analysis of Susceptible and Resistant Escherichia coli under Antibiotic Stress
17:00 - 17:20		T31	Sophia Santos, Sara Correia and Isabel Rocha	Inferring optimal minimal media for genome-scale metabolic models using evolutionary algorithms
17:45 - 19:30	2nd floor		Poster session beginning with Lightning poster talks	
20:00			Conference dinner in restaurant "Rozengrāls"	

			Friday, 16th of August	
	Room 106		Session 6.1 Methodology and mathematical algorithms and software, Chair Oliver Ebenhoeh	
09:00 - 09:35		I9	Invited speaker - Anne Siegel	Using automated reasoning to explore unconventional organisms: a first step to explore host-microbial interactions
09:35 - 09:55		T32	Alon Stern, Tomer Shlomi, Boris Sarvin, Won Dong Lee and Elina Aizenshtein	Inferring subcellular compartmentalized flux in cancer cells: A new approach integrating isotope tracing with thermodynamic analysis
09:55 - 10:15		T33	Mattia G. Gollub and Jörg Stelling	Probabilistic Integration of Flux Constraints and Thermodynamic Data in Metabolic Models
10:15 - 10:35		T34	Roland Sauter and Ines Heiland	Estimating the Impact of Cofactor Concentration Changes in Genome-scale Models
10:35 - 11:00	2nd floor		Coffee break	
	Room 106		Session 6.2 Methodology and mathematical algorithms and software, Chair Ross Carlson	
11:00 - 11:20		T35	Johann Rohwer, Carl Christensen and Jan-Hendrik Hofmeyr	PySCeSToolbox: providing deeper insight into the regulatory behaviour of kinetic models
11:20 - 11:40		T36	Sergio Garcia and Cong Trinh	Solving the Modular Cell Biocatalyst Design Problem with Multi-objective Evolutionary Algorithms
11:40 - 12:00		T37	Ana Bulović, Stephan Fischer, Edda Klipp, Vincent Fromion and Anne Goelzer	Automated creation of bacterial resource allocation models
12:00 - 12:20		T38	Christian Lieven, Moritz Beber and Nikolaus Sonnenschein	Memote: A community-driven effort towards a standardized genome-scale metabolic model test suite
12:20 - 12:40	Room 106		Closing remarks	
12:40 - 14:00	2nd floor		Lunch	
14:00 - 19:00			Departures	

Invited speakers

I1

Harald H. H. W. Schmidt
Maastricht University, The Netherlands

Title: The End of Medicine as We Know It

Abstract: Existing drugs fail to provide benefit for most patients. The efficacy of drug discovery is in a constant decline. This poor translational success of biomedical research is due to false incentives, lack of quality/reproducibility and publication bias. The most important reason, however, is our current concept of disease, i.e. mostly by organ or symptom, not by mechanism. Systems Medicine will lead to a mechanism-based redefinition of disease, precision diagnosis and therapy eliminating the need for drug discovery and a complete reorganization of how we teach, train and practice medicine.

I2

Adil Mardinoglu
KTH-Royal Institute of Technology; King's College London, Sweden and the United Kingdom

Title: The use of systems biology in treatment of liver diseases

Abstract: To develop novel strategies for prevention and treatment as well as to gain detailed insights about the underlying molecular mechanisms of liver diseases, it is vital to study the biological functions of liver and its interactions with other tissues and gut microbiota. Biological networks can provide a scaffold for studying biological pathways operating in the liver in connection with disease development in a systematic manner. In my presentation, I will present our recent work where biological networks have been employed to identify the reprogramming in liver physiology in response to NASH/NAFLD. I will further discuss how this mechanistic modelling approach can contribute to the discovery of biomarkers and identification of drug targets which may lead to design of targeted and effective treatment strategies.

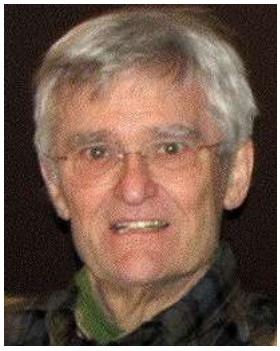
I3

Kathrin Thedieck
University of Innsbruck, Austria

Title: Systems approaches to metabolic signaling

Abstract: The kinase network converging on mTOR (mammalian/mechanistic target of rapamycin) is at the center of metabolic control in cells and organisms. Embedded in a multiply intertwined, highly dynamic network, mTOR governs the cellular response to nutrients, growth factors and stress and promotes cellular growth and survival. mTOR dysregulation has been reported for many diseases related to metabolism and ageing, including cancer, neurodegeneration and hereditary disorders. Toward the development of disease mechanism-driven personalized therapies, we develop systems approaches to metabolic control by kinase networks. This talk will focus on mTOR's stress response and cover our latest advances toward a systems understanding of metabolic signaling.

I4



Athel Cornish - Bowden
CNRS, Marseilles, France

Title: Modern Theories of Life

Abstract: There are at least five modern theories of life: Robert Rosen's (M,R) systems, Manfred Eigen and Peter Schuster's hypercycle, Tiboor Gánti's chemoton, Humberto Maturana and Francisco Varela's autopoiesis and Stuart Kauffman's autocatalytic sets. These were developed essentially independently of one another and the degree of overlap between them is far from obvious, so they seem more different from one another than they really are. They all lack an important idea that is absolutely necessary for preventing the systems they propose from degenerating into a disorganized tar: they all lack any notion of feedback regulation.

I5

Herbert Sauro
University of Washington, United States

Title: A menagerie of systems biology standards with a special focus on the Synthetic Biology Open Language

Abstract: Over the years a wide variety of standards have been developed to make computational studies in systems biology more reproducible, reusable and comprehensible. This talk will cover some of the major efforts in this area but with a special emphasis on the synthetic biology open language, SBOL. Synthetic biology builds upon the techniques and successes of genetics, molecular biology, and metabolic engineering by applying engineering principles to the design of biological systems. These principles include standardization, modularity, and design abstraction. The field still faces substantial challenges, including long development times, high rates of failure, and poor reproducibility. A common factor of these challenges is the exchange of information about designed systems between laboratories. The Synthetic Biology Open Language (SBOL) has been developed as a standard to support the specification and exchange of biological design information in synthetic biology.

I6

John Wain
Quadram Institute, United Kingdom

Title: Changing Culture in Microbiology

Abstract: The Quadram Institute in Norwich, UK is a brand new One Health focused research institute within which I lead a department called “Microbes in the Food Chain”. We are funded through a strategic programme grant from the BBSRC (UK government).

My realisation of our ability to interrogate metabolic networks came in the late nineties and drove me to lobby for the whole genome sequencing of the human restricted pathogen I was working on - Salmonella Typhi. My first PhD student (Gemma Langridge, QI) built a database from the genome sequence (and associated annotation) using Pathway Tools Software whilst the team (led by Keith Turner, QI) developed a genome wide knock-out system (TraDIS). We then used these powerful tools to show that pseudogenes where not “pseudo” at all and that small RNAs where key to the host adaptation/restriction of S. Typhi. Gemma then took this work further describing the evolutionary processes of adaptation of Salmonella to chickens through selection (for or against) of metabolic diversity and investigating the metabolic basis of human host restriction in Paratyphi. This work led my group to develop an MLST scheme for Salmonella as a replacement for serotyping which is now implemented for national public health surveillance. From what we have learned from this we are investigating the most effective way to group Salmonella (Marie Chattaway, PHE) and non-aureus staphylococci (Teresa Diaz-Calvo, QI) into robust clusters with biological relevance.

Finally, I will present work by Dipali Sing and Noemi Hernandez, QI on the use of GEMs to help design a diagnostic media for the selective growth of Campylobacter, and, if time, touch on the use of ATP metabolism (Ron Turner, Test&Treat) to monitor bacterial susceptibility to antibiotics, and our use of transposon mutagenesis and network analysis to elucidate mechanisms of resistance to antibiotics.

I7

Uwe Sauer
Institute of Molecular Systems Biology, ETH Zurich, Switzerland

Title: Metabolic Coordination Through Metabolite-Protein Interactions

Abstract: How do bacteria know what goes on in their environment and how to they make appropriate decisions? While some bona fide extracellular sensors are known, there are far more environmental conditions and cellular responses than could possibly be dealt with through dedicated sensors. Instead, most microbial responses are based on intracellular changes to environmental changes. One of the first affected networks to just about any extracellular change is metabolism that passively responds to nutritional or chemical/physical challenges. Since fluxes and intracellular metabolite levels respond within seconds, allosteric binding of metabolites to regulatory proteins and enzymes is a highly effective and rapid sensing mechanism. Different from well-establish methods to assess physical interaction between proteins and between proteins and nucleic acids, however, methods to assess metabolite-protein interactions are still in their infancy. At present we know on the order of 1500 unique regulatory metabolite-protein interactions (1). I will present results on experimentally mapping this network out further. The current results indicate that the known interactions are only the tip of the iceberg (2). Beyond mapping the regulation network, I will focus in this talk on the even more challenging and conceptual problem: understanding which of the many regulation mechanisms actually matter for a given adaptation to elicit an appropriate physiological system response. The surprising result for E. coli is that only very few regulation events appear to be required for a given transition, typically involving less than a handful of active regulators (3).

I8

Dong-Yup Lee
School of Chemical Engineering, Sungkyunkwan University, Republic of Korea

Title: Model-guided design and engineering of probiotic LAB system with host and microbiome interactions

Abstract: Constraint-based flux analysis is one of the well-established computational techniques for investigating cellular metabolism at systems-level under various environmental/genetic perturbations. The availability of software applications to conveniently implement it and related in silico methods has enabled the development of genome-scale models (GEMs) for more than 100 species across all three domains of life, thereby facilitating analysis of their intracellular metabolism. These models are also useful in contextualizing multi-omics data sets, thereby realizing the full potential of systems biology. In this talk, I will demonstrate their potential healthcare application via a case study of model-guided probiotic LAB design. First, we developed the genome-scale models of several lactic acid bacteria (LAB), followed by characterizing their metabolic capabilities under various diet regimes using transcriptome data, highlighting the rigid cofactor-driven metabolic nature in hetero-lactic fermentative bacteria. Subsequently, their metabolic interactions with the host and microbiome metabolic networks can be investigated to propose new strategies for personalized probiotic LAB design, thereby ameliorating lifestyle diseases such as type-2 diabetes and ulcerative colitis.

I9

Anne Siegel
Univ Rennes, Inria, CNRS, IRISA, France

Title: Using automated reasoning to explore unconventional organisms: a first step to explore host-microbial interactions

Abstract: Systems modeled in the context of molecular and cellular biology are highly difficult to model with a single calibrated numerical model. Flux optimization hypotheses have shown their tremendous ability to accuracy predict bacterial metabolism but they require a precise understanding of metabolic reactions occurring in the considered species. Unfortunately, this information may not be available for more complex organisms (for instance, eukaryotes) or hardly cultivable bacteria such as those evidenced in microbiomes with metagenomics technics. In both cases, flux-optimization based technics may not be applicable to elucidate systems functioning.

In this context, we will describe how automatic reasoning allows relevant features of an unconventional biological system to be identified despite lacks of data. We rely on Answer Set Programming, a logical programming paradigm with combinatorial optimization functionalities. We used this formalism to over-approximate the metabolic response of biological systems with steady-states of Boolean networks and solve gap-filling problems.
In this talk, we illustrate how such a formalism was useful to study the metabolism of macro-algae and point out on the putative role of host-bacterial interactions in the algal system. Ongoing applications explore the emerging field of system ecology, that is, elucidating interactions between a consortium of microbes and a host organism. As a first step in this field, we will illustrate the issue of reducing microbiomes according to expected metabolic phenotypes.

Abstracts for selected talks

T1

Silvio	Waschina	Germany	Christian-Albrechts-University Kiel
Johannes	Zimmermann	Germany	Christian-Albrechts-University Kiel
Julia	Pagel	Germany	Departement of Pediatrics, University Hospital Lübeck
Christoph	Kaleta	Germany	Christian-Albrechts-University Kiel

Title:	**Elucidating the metabolic processes within the gut microbiome that precede sepsis in preterm infants and remission in IBD patients**
Author keywords:	Gut, Microbiome, Flux balance analysis, Preterm infant, Dysbiosis, Bacterial metabolism
Abstract:	Gut dysbiosis has been suggested as a major risk factor for the development of inflammatory diseases including inflammatory bowel disease (IBD) and sepsis. In preterm infants, late onset sepsis (LOS) is a major cause of mortality. The sepsis-causing pathogens are commonly of intestinal origin, suggesting that the function of the gut microbiome can trigger the development of LOS. We used metagenomic sequencing of stool samples from 235 preterm infants to profile the development of the gut microbiome within the first month of life. Based on this data, bacterial community-scale metabolic models were constructed to predict the biochemical processes carried out by the microbiome. The in-silico simulations suggested an accumulation of the fermentation products ethanol and formic acid in LOS cases already before the onset of disease. This accumulation might lead to disruption of the mucosal barrier and translocation of luminal contents. Furthermore, the data shows that the production of those compounds can be attributed to Bacilli, while a lower production was predicted for microbiomes, which have a higher abundance of Bifidobacteria – a genera considered beneficial. In a similar approach, we investigated the impact of microbiome metabolism on the etiopathology of IBD. We found that metabolic cross-feeding interactions between different taxa are predominantly reduced in patients, who do not show signs of remission following anti-TNFα treatment compared to remitters or healthy controls. Thus, the results could guide novel individualized prevention strategies of inflammatory diseases for example by pro- and prebiotics administration that target the metabolic function of the gut microbiome.

T2

Germán Andres	Preciat Gonzalez	Netherlands	Leiden University
Luojiao	Huang	Netherlands	Leiden University
Emma	Schymanski	Luxembourg	University of Luxembourg
Thomas	Hankemeier	Netherlands	Leiden University
Ronan	Fleming	Netherlands	Leiden University
Title:	**Atom mapping data for genome-scale metabolic network reconstructions; Application in human dopaminergic neuronal metabolism**		
Author keywords:	Genome-scale metabolic models, Constraint-based modeling, Neuroepithelial stems cells, Conserved moieties, Tracer based experiments		
Abstract:	Patient-derived cellular models are a powerful tool to study neurodegenerative diseases, such as Parkinson's Disease, where affected primary neurons, such as substantia nigra dopaminergic neurons, are almost inaccessible. Induced pluripotent stem cell-derived models of midbrain-specific dopaminergic neurons are increasingly used to investigate Parkinson's Disease. In previous work, we reported the first genome-scale constraint-based model of metabolism in human neuroepithelial stem cell-derived dopaminergic neurons, denoted as the iNESC2DN model. Here we investigate a more detailed representation of metabolism at the level of atom mappings. This approach opens the possibility for a broader range of biological, biomedical and biotechnological applications than with stoichiometry alone. We standardised molecular structures in the Virtual Metabolic Human database and computed standardised atom mappings for the majority (1,169/1,608) of the metabolic reactions in the iNESC2DN model. Furthermore, we identified a set of conserved moiety vectors that form a sparse non-negative integer basis for the left null space of the stoichiometric matrix. This enabled us to predict the possible paths of each moiety through a metabolic network. Conserved moiety vectors were used to design novel tracer-based metabolomic experiments in dopaminergic neurons. ReconMap3 was used to visualise the molecules, and their corresponding pathways, that had the potential to be isotopically labelled by each potential tracer. Our work lays the foundation for genome-scale tracer-based metabolomic experiments in dopaminergic neurons based on the optimal design of the most suitable tracers and metabolites to target in the development of a complementary analytical chemistry platform.		

T3

Jean-Marc	Schwartz	United Kingdom	The University of Manchester
Zita	Soons	Netherlands	Maastricht University
Title:	**Fluxomics reveals cellular and molecular basis of increased renal ammoniagenesis**		
Author keywords:	Elementary flux mode, Gene expression, Ammoniagenesis		
Abstract:	The kidney plays a critical role in excreting ammonia during metabolic acidosis and liver failure, but the mechanisms behind this process have been poorly explored. Hereto, we fed eight rats an amino acid-rich diet (HD group) and eight a normal chow diet (AL group). We developed a computational method based on elementary mode analysis to study changes in amino acid flux occurring across the kidney in increased ammoniagenesis. First, we found that total renal ammoniagenesis increased 2.3 fold in the HD group with a concomitant up-regulation of ammonia transporters (NKCC2, NHE3, ASCT2, NKCC2, SNAT-3). We reconstructed a kidney specific model of central metabolism in postabsorptive state (AL group) and used structural fluxes to predict flux distributions under different cellular objectives. The best correlations with measured fluxes were obtained with ammonia transport as an objective, followed by growth, protein uptake, urea excretion, and lysine and phenylalanine transport. These predictions were improved when specific gene expression data were taken into account in HD conditions assuming that only the pathways containing significantly up-regulated gene(s) were active. This suggests that the mitochondrial glycine pathway might be involved in increased renal ammoniagenesis.		

T4

Darta	Zake	Latvia	Latvian Biomedical Research and Study Centre
Egils	Stalidzans	Latvia	Latvian Biomedical Research and Study Centre
Linda	Zaharenko	Latvia	Latvian Biomedical Research and Study Centre
Janis	Klovins	Latvia	Latvian Biomedical Research and Study Centre

Title:	**Physiologically based metformin pharmacokinetics model for estimation of therapeutic concentrations in various tissues**
Author keywords:	Physiologically based pharmacokinetic modeling, Metformin, Mathematical modeling, Type 2 Diabetes
Abstract:	International treatment guidelines recommend metformin to be the first-line medication in nearly all newly diagnosed Type 2 Diabetes patients and currently used by over 120 million patients worldwide.While the doses of metformin used in therapy range from 500 mg up to 3000 mg, the effective therapeutic concentrations in major compartments of metformin action (such as the intestine, liver, muscle and adipose tissue) have not been measured in humans. Thus, adequate dosage and how often drug is administered for an individual to reach therapeutic metformin concentrations in particular tissues has not been determined or even estimated. A general model of metformin pharmacokinetics was built as a system of ordinary differential equations (ODE) that describes the transport of administered metformin through tissues and body fluids. The model describes metformin transport and concentrations in various tissues over time in a healthy human. Model was created using COPASI software that enables parameter estimation with several experimental data sets at the same time. Modeling of metformin pharmacokinetics of healthy humans was performed by integrating experimental metformin concentration time courses from study of metformin transport in plasma, pre-urine and urine in humans and experimental metformin concentration time courses about proportions of metformin distribution in different mouse tissues. This research will enable further development of individually parameterized model that can consider metformin transport and excretion peculiarities of individuals. Special attention is paid to the metformin exchange between plasma and erythrocytes to parametrize features of transport proteins.

T5

Thomas	Sauter	Luxembourg	University of Luxembourg
Tamara	Bintener	Luxembourg	University of Luxembourg
Dominik	Ternes	Luxembourg	University of Luxembourg
Dagmar	Kulms	Germany	TU Dresden
Serge	Haan	Luxembourg	University of Luxembourg
Elisabeth	Letellier	Luxembourg	University of Luxembourg
Maria Pires	Pacheco	Luxembourg	University of Luxembourg
Title:	**Identifying and targeting cancer-specific metabolism with network-based drug target prediction**		
Author keywords:	Metabolic modeling, Drug Repurposing, Cancer, Machine learning		
Abstract:	Background: Metabolic rewiring allows cancer cells to sustain high proliferation rates. Thus, targeting only the cancer-specific cellular metabolism will safeguard healthy tissues. Methods: We developed the very efficient FASTCORMICS RNA-seq workflow (rFASTCORMICS) to build 10 005 high-resolution metabolic models from the TCGA dataset to capture metabolic rewiring strategies in cancer cells. Colorectal cancer (CRC) was used as a test case for a repurposing workflow based on rFASTCORMICS. Findings: Alternative pathways that are not required for proliferation or survival tend to be shut down and, therefore, tumours display cancer-specific essential genes that are significantly enriched for known drug targets. We identified naftifine, ketoconazole, and mimosine as new potential CRC drugs, which were experimentally validated on patient derived CRC cell lines. Interpretation: The here presented rFASTCORMICS workflow successfully reconstructs a metabolic model based on RNA-seq data and successfully predicted drug targets and drugs not yet indicted for colorectal cancer.		

T6

Stefan	Mueller	Austria	University of Vienna, Faculty of Mathematics
Georg	Regensburger	Austria	JKU Linz
Juergen	Zanghellini	Austria	BOKU WIne

Title:	**Flux tope analysis: which combinations of reaction directions are (thermodynamically) feasible?**
Author keywords:	Thermodynamic feasibility, Gibbs free energy, Elementary flux mode, Flux tope, Sign vector, Hyperplane arrangement
Abstract:	A flux tope (FT) is a subset of the flux cone specified by fixing the directions of all reversible reactions. Whereas elementary flux modes (EFMs) represent 'minimal pathways', every FT contains a 'maximal pathway', carrying flux in all reactions. A thermodynamically feasible FT represents one possible combination of reaction directions and contains all corresponding pathways. Thereby, the thermodynamic feasibility of a FT is determined by the metabolite concentrations via the Gibbs free energy. Via cellular control of the metabolite concentrations, a FT can be reached and the corresponding pathways can be activated. Ultimately, FT analysis can be used to study the coordination of reaction directions in genome-scale metabolic models (GSMMs), that is, the 'thermodynamic repertoire' of cellular metabolism. To develop a mathematical framework for FT analysis, we build on the concepts of sign vectors and hyperplane arrangements. Thereby, we observe that FT analysis can be applied also to flux optimization problems involving additional linear constraints. For the enumeration of FTs, we adapt the reverse search algorithm and provide an efficient implementation. As it turns out, FTs can be used to enumerate EFMs in GSMMs with reversible reactions. Indeed, FTs can be computed first, and EFMs (of individual FTs) can be enumerated efficiently (without increasing the problem dimension by reaction splitting) in a second step. doi: 10.1093/bioinformatics/bty550

T7

José P.	Faria	United States	Argonne National Laboratory
Filipe	Liu	United States	Argonne National Laboratory
Janaka N.	Edirisinghe	United States	Argonne National Laboratory
Samuel M.D.	Seaver	United States	Argonne National Laboratory
James G.	Jeffryes	United States	Argonne National Laboratory
Qizh	Zhang	United States	Argonne National Laboratory
Pamela	Weisenhorn	United States	Argonne National Laboratory
Boris	Sadkhin	United States	Argonne National Laboratory
Nidhi	Gupta	United States	Argonne National Laboratory
Tian	Gu	United States	Argonne National Laboratory
Christopher	Henry	United States	Argonne National Laboratory
Title:	**High Throughput Genome-Scale Metabolic Model Reconstruction and Reconciliation with Tn-seq Data**		
Author keywords:	Genome-scale metabolic models, Model reconstruction, Gapfilling, ModelSEED		
Abstract:	The Department of Energy Systems Biology Knowledgebase (KBase) is a platform designed to solve the grand challenges of Systems Biology. KBase has implemented bioinformatics tools that allow for multiple workflows including genome annotation, comparative genomics, and metabolic modeling. In KBase, we selected a phylogenetically diverse set of approximately 1600 genomes and constructed draft genome-scale metabolic models (GEMs) using the ModelSEED pipeline implemented in KBase. We used these 1600 genomes as a test set to improve the quality of models produced by the ModelSEED. First, we updated our biochemistry database to include reaction data from KEGG, MetaCyc, BIGG and published models. In an effort to reconcile pathway representation across the multiple databases, we manually curated pathways, before inclusion in our reconstruction templates. Next, we curated our mapping of RAST functional roles to biochemistry by reconciling with data mined from KEGG and published metabolic models; we corrected errors in our reaction reversibility assertions to improve overall model constraints; we refined our gapfilling procedure to prevent draft models from our pipeline from over-producing ATP; we show how all of our pipeline improvements increase the number of gene associations, decrease the number of gapfilled reactions, improve the accuracy of growth and ATP production yield predictions, and decrease the number of blocked reactions across all models. Finally, we select 25 specific genomes for which comprehensive TN-seq data is available, and we compare model predictions of all data with experimental results, showing significant improvement in accuracy between models generated by the original ModelSEED.		

T8

Tin Yau	Pang	Germany	Heinrich Heine University Duesseldorf
Martin	Lercher	Germany	Heinrich Heine University Duesseldorf
Title:	**Natural selection on the extent of intracellular crowding**		
Author keywords:	Molecular crowding, Metabolic network, Evolution		
Abstract:	Proteins, metabolites, and other macromolecules constitute a substantial portion of the cytosol. The cell can control the level of the resulting molecular crowding by controlling the transport of different molecular species and of water into and out of the cell. An increase in molecular crowding slows down diffusion of molecules within the cytosol and may thus reduce metabolic fluxes. However, molecular crowding may also influence metabolic fluxes through strengthening the excluded volume effect—the interaction between metabolites and macromolecules due to their non-zero volume—and through affecting the Gibbs free energies of substrates, enzymes, and substrate-enzyme complexes. Here, we hypothesize that maximal growth of a cell is facilitated by an intermediate crowding level. Thus, under natural selection, cells would organize their solutes to occupy a constant fraction of the cytosolic volume, as is observed in E. coli across different growth conditions. To quantify the effects of molecular crowding on cellular growth, we stimulated the growth of a simple, coarse-grained cell model at different cytosol densities. Our model systematically accounts for the change in Gibbs free energy and the slowdown of diffusion caused by molecular crowding. We observe that optimal cytosol density depends strongly on the kinetic properties of the reactions. Optimal growth occurs at intermediate cytosol occupancy, as observed experimentally.		

T9

John	Barrett	United States	University of Minnesota
Friedrich	Srienc	United States	University of Minnesota
Title:	**Statistical Thermodynamics of Metabolic Reaction Networks**		
Author keywords:	Metabolic network, Elementary flux modes, Maximum entropy production principle, Evolution		
Abstract:	A glucose molecule entering a cell is always metabolized along a pathway trajectory that is represented by a reaction sequence known as Elementary Flux Mode (EFM). These fundamental pathways can be rigorously computed from the stoichiometric network model. Thus, the identification and enumeration of all possible EFMs effectively represents a discretization of the metabolic network since the metabolic conversion of individual glucose molecules can only occur along the discrete pathways represented by EFMs. The determination of the probabilities for glucose molecules to use individual EFMs represents a significant challenge in quantifying the rate structure of a metabolic network. We have developed the macroscopic theory that proves the maximum entropy production principle for an open, reacting system in a stationary state in which the Gibbs free energy is minimized. At the molecular level we show that the usage probabilities of individual EFMs can be computed from the entropy production rates of individual pathway trajectories which are distributed according to a Boltzmann distribution when the macroscopic entropy production rate is maximized. We have validated the theory by predicting the experimentally determined metabolic rate structure of adaptively evolved E. coli strains. Thus, the dynamic properties of such bacteria can be predicted in principle just from the knowledge of the DNA sequence of the organism from which the metabolic reaction network can be reconstructed.		

T10

Filipe	Liu	United States	Argonne National Laboratory
Samuel M.D.	Seaver	United States	Argonne National Laboratory
José P.	Faria	United States	Argonne National Laboratory
Janaka N.	Edirisinghe	United States	Argonne National Laboratory
James G.	Jeffryes	United States	Argonne National Laboratory
Tian	Gu	United States	Argonne National Laboratory
Christopher	Henry	United States	Argonne National Laboratory
Title:	**Validation and Curation of Biochemical Networks through thermodynamics and visualization**		
Author keywords:	Databases, Data integration, Metabolic networks, Model reconstruction, Genome-scale metabolic models		
Abstract:	The ModelSEED biochemistry is the foundation of the ModelSEED reconstruction approach, which is integrated into many metabolic reconstruction protocols. It consists a merger between major biochemistry resources, but also assimilates several published models. However, integration challenges and inconsistencies are common to such databases and ModelSEED is no exception. In our latest update, additional curation protocols were implemented in order to solve many issues related to "reconciled" databases. Traditional metrics often rely on the presence of compound attributes (e.g., structures) to evaluate the success of the integration. However, it is known that many entities (e.g., macromolecules) have ill-defined or ambiguous molecular structures, resulting in mistakes during structure-based integration. In our work, we leverage the Escher tool for drawing and visualizing biochemical networks to construct comparative views of common pathways across many source databases, enabling us to rapidly identify and correct inconsistencies in the biochemistry. In the process, we created new pathway layouts and expanded existing layouts. We use this semi-automated approach to identify gaps, duplicates, inconsistencies, and other errors that are common to automated integration approaches. We constructed an ontology to describe and link compounds and reactions that are equivalent but not identical among the databases. The maps created are available for use as a pathway browser for the ModelSEED biochemistry and template model system. We also use thermodynamics as a curation tool to report irregular energies in our reactions as an additional verification. Our thermodynamic analysis included a useful update of the thermodynamic values in our biochemistry database using Equilibrator.		

T11

Nima	Saadat	Germany	Heinrich Heine University, Düsseldorf
Ovidiu	Popa	Germany	Heinrich Heine University, Düsseldorf
Title:	**Impact of prophage encoded enzymes on the metabolic capacity of the hosts.**		
Author keywords:	Bacteria, Phage, Metabolic Network, Network Expansion, Horizontal Gene Transfer		
Abstract:	Phages are viruses that infect specific bacteria and archaea. Upon infection the phage can either enter the lytic cycle or the lysogenic cycle. In the lytic cycle the phage replicates and destroys the host cell, whereas in the lysogenic cycle the phage integrates into the host genome (now called prophage). In this dormant state the prophage is distributed in the population by host replication. The prophage can re-enter the lytic cycle and during phage replication parts of host genetic material can be acquired by the phage genome. This acquired genetic material is integrated into new hosts after phage infection followed by the lysogenic cycle. Bacterial genetic material transfer by phages is one mechanism of horizontal gene transfer with consequences for the host genome. Fitness enhancing or decreasing effects of prophage associated genes in bacteria are controversially discussed. In our work, we investigate the impact of prophage associated genes encoding for metabolically active enzymes on assembled metabolic networks of corresponding hosts. Based on the BioCyc database we build metabolic network assemblies of 323 bacterial genomes, for which we identified 2700 prophages containing metabolically active enzymes, and calculate differences in metabolic network capacities using the network expansion algorithm. Our finding suggests that prophage encoded metabolic enzymes have significantly less impact on the metabolic capacity of the hosts as expected by chance. This observation is constant across the host taxonomic borders suggesting that phage mediated gene transfer is less likely to provide an enhanced fitness to the host metabolism.		

T12

Ashley	Beck	United States	North Carolina State University
Tomas	Gedeon	United States	Montana State University
Jeffrey	Heys	United States	Montana State University
Ross	Carlson	United States	Montana State University
Title:	**Surface area is a cellular resource that can be used to predict and design competitive biological organization**		
Author keywords:	Membrane surface area, Substrate cometabolism, Cross-feeding consortia		
Abstract:	Understanding and controlling biological systems requires an understanding of their physical constraints. Microorganisms have limited surface area to interact with the environment. This constraint, based on cellular dimensions and geometry, is hypothesized to be optimized for competitive ecological function. Escherichia coli demonstrates different metabolic motifs including overflow, diauxie, or cometabolism when grown on permutations of glucose, lactate, and acetate. These behaviors can be rationally explained and predicted using a cellular surface area optimization criterion. Cellular surface area is a resource and constraint that can be rationally exploited. Limitations on monoculture surface area can be overcome through cross-feeding consortia. Consortia designed for glucose catabolism with acetate or lactate cross-feeding were designed and constructed. The design effectively partitioned the use of cellular surface area between two interacting populations, permitting enhanced glucose consumption, higher glucose conversions, and higher biomass and lower inhibitory byproduct accumulation. Knowledge of basic geometrical constraints can guide the design of improved bioprocess strategies and provide insight into natural microbial community organization.		

T13

Marian	Breuer	United States	University of Illinois at Urbana-Champaign
Tyler	Earnest	United States	University of Illinois at Urbana-Champaign
Chuck	Merryman	United States	J. Craig Venter Institute
Kim	Wise	United States	J. Craig Venter Institute
Lijie	Sun	United States	J. Craig Venter Institute
Michaela	Lynott	United States	J. Craig Venter Institute
Clyde A.	Hutchison Iii	United States	J. Craig Venter Institute
Hamilton	Smith	United States	J. Craig Venter Institute
John	Lapek	United States	University of California San Diego
David	Gonzalez	United States	University of California San Diego
Valerie	De Crecy-Lagard	United States	University of Forida
Drago	Haas	United States	University of Florida
Andrew D.	Hanson	United States	University of Florida
Piyush	Labhsetwar	United States	University of Illinois at Urbana-Champaign
John	Glass	United States	J. Craig Venter Institute
Zaida	Luthey-Schulten	United States	University of Illinois at Urbana-Champaign
Title:	**Essential metabolism for a minimal cell**		
Author keywords:	Minimal cell, Metabolic reconstruction, Flux balance analysis, Transposon mutagenesis, Mycoplasma		
Abstract:	The question of the core requirements of cellular life led to the construction of the "minimal cell" JCVI-syn3A: A cell where practically all genes were removed that were not essential for robust growth in a stress-free laboratory environment. With only 493 genes in a 543 kbp genome, JCVI-syn3A has a genome smaller than that of any independently-replicating cell found in nature. It provides a versatile platform to study the basics of cellular life and is small enough that a complete description of all cellular functions can be pursued. Here, we present an extensively curated metabolic reconstruction and flux balance analysis (FBA) model of this minimal cell, using the vast amount of experimental information available on its natural precursor, Mycoplasma mycoides capri. The model, featuring 339 reactions involving 305 metabolites, is near-complete with 98 % of enzymatic reactions justified through gene assignments and/or experimental evidence, and agrees well with gene essentiality data from transposon mutagenesis experiments. The 155 genes included in the reconstruction have a high in vivo essentiality or quasi-essentiality of 92 %, compared to 79 % in silico essentiality-underscoring the minimality of the network. The reconstruction itself and the comparison of in vivo and in silico essentialities lead to new hypotheses on particular metabolic functions, suggesting specific experiments. Thus, the model provides a solid foundation for further experimental and computational studies on the minimal cell.		

T14

Mikk	Õun	Estonia	TFTAK
Nikita	Rom	Estonia	TFTAK
Raivo	Vilu	Estonia	TFTAK
Vassili	Kiritsenko	Estonia	TFTAK
Kristo	Abner	Estonia	TFTAK
Taivo	Lints	Estonia	TFTAK
Maria	Bubina	Estonia	TFTAK
Title:	**A Novel Tool for Metabolic Model Optimisation and Result Visualisation**		
Author keywords:	Flux balance analysis, Optimisation, Metabolic networks, Data visualization, Data analysis		
Abstract:	In 1984 Watson published the first article describing linear programming methods for Flux Balance Analysis. Since then optimisation methods have evolved into elaborate systems capable of producing massive amounts of data. However, one of the biggest problems of the big data era is making sense of the calculated results. While methods applied to network analysis, as well as the models optimised differ, the output data shape remains unchanged. A skilled bioinformatician is capable of transforming the data and swiftly drawing conclusions, while it can be a challenge for a wet-lab biologist. In an effort to popularise biological systems modelling we have developed a user-friendly environment capable of model optimisation and result visualisation. Contributing to open source Escher and CobraPy software, we developed a novel network analysis service singlecellmodel.com. It allows users to run large quantities of network simulations, test different fixed conditions, as well as vary parameters in ranges thus assessing impact on the system. Concentrating on the intuitive design, our environment allows construction of pseudo 4-dimensional graphics for multiple parameter comparison. Each optimisation result can be viewed on a network map (Escher), giving an additional overview of the system. Availability The software environment described above is available from singlecellmodel.com		

T15

Steffen	Klamt	Germany	Max Planck Institute for Dynamics of Complex Technical Systems
Simon	Boecker	Germany	Max Planck Institute for Dynamics of Complex Technical Systems
Ahmed	Zahoor	Germany	Max Planck Institute for Dynamics of Complex Technical Systems
Title:	**Extending the Scope of Enforced ATP Wasting as a Tool for Metabolic Engineering in Escherichia coli**		
Author keywords:	Metabolic Engineering, Metabolic Modeling, Energy Metabolism, Systems Biotechnology		
Abstract:	The targeted increase of cellular ATP turnover (enforced ATP wasting) has been recognized as a promising tool for metabolic engineering when product synthesis is coupled with net ATP formation. Here we further examined and further developed the concept of enforced ATP wasting to broaden its scope for potential applications in biotechnology. In an initial model-driven study, we first demonstrated that methods such as enforced ATP wasting are vital for the performance (volumetric productivity) of bioprocesses, especially in two-stage processes where growth and product synthesis are decoupled. We then developed a new genetic module for dynamic and gradual induction of the F1-part of the ATPase and thus of uncoupled ATP hydrolysis in E. coli. Considering the fermentation products of E. coli as a proxy for target chemical(s), we then found that induction of the ATPase leads to (a) higher metabolic activity and increased product formation in E. coli growing under anaerobic conditions and (b) to significantly increased substrate uptake and productivity of growth-arrested cells. To the best of our knowledge, the glucose uptake rate of 6.49 mmol/gCDW/h achieved with enforced ATP wasting is the highest value reported for non-growing E. coli cells holding great potential for two-stage processes. In summary, we showed that enforced ATP wasting may improve yield and titer (in growth-coupled processes) as well as volumetric productivity (in two-stage processes) depending on which of the performance measures is more crucial for the process and product of interest. Boecker, Zahoor, Klamt (2019), Biotechnology Journal, in press.		

T16

Debolina	Sarkar	United States	The Pennsylvania State University
Costas	Maranas	United States	The Pennsylvania State University
Title:	**SNPeffect: Identifying Functional Roles of SNPs using Metabolic Network**		
Author keywords:	Kinetic model, Parameter estimation, Genome-scale, Steady state, Fluxomics		
Abstract:	Genetic sources of phenotypic variation have been a major focus of studies in plants aimed at improving agricultural yield and understanding adaptive processes. Genome-wide association studies (GWAS) aim to identify the genetic background behind a trait by examining the associations between specific phenotypes and single-nucleotide polymorphisms (SNPs). Although such studies are now commonly performed, biological interpretation of the results remains a challenge; especially due to the confounding nature of population structure and the systematic biases it introduces. Here, we propose a complementary analysis referred to as SNPeffect that sifts out functional SNPs from the tens of thousands typically identified during a genome sequencing study by integrating biochemical knowledge encoded in metabolic models, superimposed with phenotypic measurements. By design, SNPeffect can handle both monogenic and polygenic traits while offering mechanistic interpretations of the deciphered genotype-to-phenotype relations. SNPeffect was used to explain phenotypic variations such as differential growth rate and metabolite accumulation in A. thaliana and P. trichocarpa accessions as the outcome of activating and inactivating SNPs present in the enzyme-coding regions of the genotypes. To this end, we also constructed a non-compartmentalized genome-scale metabolic model for Populus trichocarpa, the first for a perennial woody tree. As expected, our results indicate that plant growth is a complex polygenic trait which is primarily governed by carbon and energy partitioning. Growth-affecting SNPs in coding regions were found to primarily be in amino-acid metabolism, glycolysis, TCA cycle, and energy metabolism.		

T17

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Maximilian	Fichtner	Germany	Dept. of Bioinformatics, University of Jena
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Title:	**How to cope with the combinatorial complexity of fatty acids?**		
Author keywords:	Fatty acid synthesis, Fibonacci numbers, Golden ratio, Lipidomics, Oxolipids, Synthetic biology		
Abstract:	Lipid biosynthesis is a complex subsystem of metabolism, because of the chain elongation reactions of fatty acids (FAs) and the variability in the composition of different phospholipids, triglycerides, etc. [1]. A fundamental question is how the potential number of FAs (with varying numbers of double bonds) increases with their chain length. Due to the synthesis mechanism, most FAs involve an even number of carbons. However, odd-chain FAs also occur, for example, pentadecanoic acid (15:0) in cow milk or pelargonic acid (9:0) and valeric acid (5:0) in some plants. Here, we show that the potential number of unbranched FAs grows according to the famous Fibonacci numbers when cis/trans isomerism is neglected and adjacent double bonds are excluded [2]. Since the ratio of two consecutive Fibonacci numbers tends to the Golden section, 1.618, organisms can increase fatty acid variability approximately by that factor per carbon atom invested. Moreover, we show that, under consideration of cis/trans isomerism and/or of modification by hydroxy and/or oxo groups, diversity can be described by generalized Fibonacci numbers (e.g. Pell numbers) [2]. Similar calculations can be performed for aliphatic amino acids [3]. Our results should be of interest for synthetic biology, combinatorial chemistry, mass spectrometry, patent applications, use of fatty acids as biomarkers and the theory of evolution. References [1] D. Kenanov, …, S. Schuster. FEBS J. 277 (2010) 1023-1034. [2] S. Schuster, M. Fichtner, S. Sasso. Sci. Rep. 7 (2017) 39821 [3] M. Fichtner, K. Voigt, S. Schuster. Biochim. Biophys. Acta - Gen. Subj. 1861 (2017) 3258-3269		

T18

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Title:	**In silico exploration of paths toward C4 metabolism**
Author keywords:	C3 photosynthesis, C4 photosynthesis, Photosynthetic nitrogen-use efficiency, C4 evolution, C4 ecology, Leaf nitrogen level, Flaveria, Environment
Abstract:	Metabolic efficiency is an important determinant of organismal fitness. To ensure optimal efficiency, limiting resources such as nitrogen need to be balanced in response to environmental conditions. Photosynthesis is particularly suited to explore the interplay between environmental factors and metabolism. Its key enzyme Rubisco catalyzes the reaction with either CO2 or O2. The unwanted reaction with O2 results in the costly photorespiratory pathway; in the ancestral C3 plants, photorespiration is prompted by factors like high temperatures. C4 plants, which evolved from C3 plants multiple times, employ a mode of photosynthesis that uses an energy-consuming CO2 concentrating mechanism to suppress photorespiration. However, the quantitative effect of environmental factors on the cellular resource allocation is not yet understood; it is also unclear how nitrogen availability may have influenced C4 evolution. To address these questions, we developed a comprehensive mathematical model that considers C3, C3-C4 intermediate, and C4 photosynthesis. This model represents the photosynthetic apparatus, accounts for photosynthetic nitrogen and energy allocation, and includes linear and cyclic electron transport. It predicts physiological parameters in response to different light intensities, leaf nitrogen levels, temperatures, and CO2 and O2 gas concentrations. We find that at lower nitrogen availability, less nitrogen needs to be re-allocated in order to transform an optimal C3 plant into an optimal C4 plant. This finding indicates that nitrogen scarcity may accelerate C4 evolution, a conclusion that is supported by simulated evolutionary trajectories. Thus, our mathematical model provides insights into the ecology of C3 and C4 plants and into C4 photosynthesis evolution.

T19

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Mark C. M.	van Loosdrecht	Netherlands	Delft University of Technology
Aljoscha	Wahl	Netherlands	Delft University of Technology
Title:	**The environment selects: Modeling intracellular energy allocation in microbial communities under dynamic environments**		
Author keywords:	Microbial communities, Storage metabolism, Metabolic switches, Dynamic resource allocation, Metabolic modeling		
Abstract:	What will be the best metabolic strategy in a competitive environment where oxygen is periodically unavailable? A few decades ago, an accidental, man-made cyclic anaerobic/aerobic environment selected for Polyphosphate Accumulating Organisms (PAOs) and this strategy is now widely used to allow for Enhanced Biological Phosphorus Removal (EBPR) of wastewater. But could it have been predicted? In this work, a dynamic resource allocation modeling formalism was used to analyze the impact of selection pressures on metabolic function. The results highlight how storage metabolism enhances metabolic strategies and allows for different trade-offs between growth yield, robustness, and competitiveness. Interestingly, the PAO phenotype is a combination of common metabolic traits; Their metabolic network can be regarded as a 'hyper-network' that also serves as a basis for demonstrating what other (more growth- and less storage-oriented) strategies may exist that are predicted to be less competitive than PAOs in specific dynamic environments. With the same network but modified selective pressures, other strategies (for instance Glycogen-AOs, Polyhydroxyalkanoate-AOs, and regular aerobic heterotrophs) can be predicted as successful metabolic strategies. This case highlights the importance of metabolic functions as a determining factor for a selective advantage in a given environment. This can be seen as an example of "Unity in biochemistry" meets "Everything is everywhere, but the environment selects" and how microbial ecosystems may be simply described by the energy allocation phenotype instead of a detailed description of each organism.		

T20

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Ahmad	A. Zeidan	Denmark	Discovery, R&D, Chr. Hansen A/S, Hørsholm, Denmark
Oscar	Dias	Portugal	Centre of Biological Engineering, University of Minho, Braga, Portugal
Title:	**What Can Multiple Genome-Scale Metabolic Models Unveil About the Same Organism? A Case Study of the Dairy Bacterium Streptococcus thermophilus**		
Author keywords:	Genome-Scale Metabolic Model, Streptococcus thermophilus LMD-9, Streptococcus thermophilus LMG18311, Dairy Bacterium, Lactic Acid Bacteria, Metabolic Network Reconstruction, Constraint-based Model		
Abstract:	The significant increase in the number of publicly available genome sequences promoted the reconstruction of Genome-Scale Metabolic (GSM) models for various microorganisms. A new reconstruction of the metabolic network of Streptococcus thermophilus was developed by using an up-to-date genome annotation of the strain LMD-9. This reconstruction was developed using merlin, a user-friendly computational tool developed in-house. The model has been manually curated with information found on literature, where strain-specific data was preferred. The shift from homo- to hetero-lactic fermentative behavior in the dairy bacterium GSM model was assessed. This analysis focused on the pyruvate-formate lyase enzyme, which contributes to controlling the fluxes around the pyruvate node. It was concluded that the GSM model can predict the dual fermentative behavior in S. thermophilus for different environmental and genetic conditions. Furthermore, three S. thermophilus LMD-9 GSM models were created with other reconstruction tools, namely ModelSEED, CarveMe and MetaDraft, and two S. thermophilus LMG18311 models were retrieved from the literature. These models together with the one developed in this work were assessed regarding their ability to identify the strains nutritional requirements. All models were evaluated for carbon source utilization, amino acids essentiality and minimal media requirements. The results were compared with information found in the literature for each strain. Strain-specific comparisons of known metabolic capabilities and model predictions were conducted to assess the capabilities of each GSM model. Overall, the GSM models retrieved from automated approaches are considerably far from predicting accurate growth phenotypes, making the improvement of such reconstructions a difficult task.		

T21

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Title:	**Modulating mitochondria horsepower for biotechnological applications**
Author keywords:	Mitochondrial metabolism, Fermentation, OxPhos, Alternative oxidase, Yarrowia lipolytica
Abstract:	Large literature studies on eukaryotic cell metabolism forced to conceptualize mitochondria as the energy powerhouse of the cell. However, recent studies and ours tend to consider mitochondria "more than just a powerhouse", otherwise, a central organelle of the cell with large spectrum of applications for biochemical reaction modulations and biomolecules productions. Thus, mitochondrial activity plays pivotal role on energetic yield and/or efficiency, especially when submitted to variable carbon concentrations. Fermentation and oxidative phosphorylation are two intertwined metabolic pathways usually considered to characterize mitochondrial efficiency. ATP yield of fermentation is much lower compared to OxPhos. Respiration to fermentation transitions occurs in optional aerobe organisms upon oxygen limitation (Pasteur effect), high rate of glycolysis (Crabtree effect) and even in cancer cells (Warburg effect). All these mechanisms are assimilated to the global overflow metabolism. In our last studies we aimed to decipher mitochondria efficiency in Yarrowia lipolytica, an obligate aerobe yeast known to produce large amount of citrate and with high capacity for intracellular lipids accumulation. Using genome-scale metabolic model of Y. lipolytica, we first characterized overflow metabolism in this oleaginous yeast and then we identified mitochondrial levers to trigger citrate overproduction. The model predicts that inhibition the alternative oxidase (AOX), a protein responsible for Y. lipolytica respiration during stationary phase, allows citrate optimization. These results were experimentally confirmed.

T22

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Paula	Gaspar	Denmark	Chr. Hansen A/S
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Title:	**Genome-scale metabolic modeling of Streptococcus thermophilus uncovers the signature of milk adaptation**		
Author keywords:	Genome-scale model, Streptococcus thermophiles, Evolution, Redox balance, Pyruvate metabolism		
Abstract:	Streptococcus thermophilus is a bacterium with major significance in the dairy industry for the production of fermented dairy products. A genome-scale model (GEM) of S. thermophilus CH8 was constructed using a pan-metabolic network approach, aided by GEMs of other organisms. The accuracy of the model was increased by applying phenotypic information, transcriptome integration and measured metabolite uptake and secretion rates as constraints, ultimately yielding similar in silico and in vitro growth rates. Simulation of growth in milk and chemically defined medium allowed the identification of flux distribution differences between peptide and amino acid nitrogen sources, while differences in redox and ATP metabolism were further identified between the two growth conditions. In an evolutionary perspective the GEM elegantly offers insight into the genomic evolution of S. thermophilus during milk adaption, providing underlying reasons for the retainment or loss of certain genes involved in metabolic reactions within e.g. pyruvate and amino acid metabolism.		

T23

Ross	Carlson	United States	Montana State
Michael	Henson	United States	UMass
Luke	Hanley	United States	U of Illinois Chicago
Matthew	Fields	United States	Montana State University
Title:	**In silico and Multi-omics analysis of Reverse Diauxie in Pseudomonas aeruginosa**		
Author keywords:	Reverse diauxie, Medical systems biology, Microbial ecology		
Abstract:	Chronic wounds are host-pathogen environments that fail to heal in a timely manner, are a major health care challenge, and cost the US more than $33 billion per year. Chronic wounds are typically colonized by multiple species, including Pseudomonas aeruginosa. P. aeruginosa is an ecologically competitive bacterium distributed globally in aquatic, terrestrial, human-built as well as medical environments. P. aeruginosa metabolism differs from common model organisms; it does not maximize its growth rate, does not catabolize glucose preferentially over other substrates, and does not utilize an 'overflow' metabolism to optimize resource investment. Despite contradicting common pillars of metabolic optimization, the organism thrives in many environments. This study uses a combination of in silico analysis, exometabolomics and label-free proteomics to quantify the P. aeruginosa carbon catabolite repression (CCR) strategy termed 'reverse diauxie'. The ecological basis of reverse diauxic metabolism was analyzed using experimental data and genome-scale metabolic models along with commonly used optimization criteria. Not surprisingly, optimization criteria like maximizing growth rate did not accurately predict P. aeruginosa physiology. The reverse diauxie CCR preference for carbon sources like succinate could be predicted accurately using a multidimensional, resource tradeoff surface that emphasizes respiration. Experiments documented reverse diauxie in both planktonic and biofilm cultures highlighting the metabolic strategy even in the presence of biofilm-associated mass transfer limitation of O2. The study provides ecological insight for interpreting P. aeruginosa growth strategies, expands systems biology tools beyond common model organisms, and provides a robust metabolic mechanism for division of labor in some microbial consortia.		

T24

Jürgen	Zanghellini	Austria	Austrian Centre of Industrial Biotechology, University of Natural Resources and Life Sciences, Vienna
Bianca	Buchner	Austria	University of Natural Resources and Life Sciences, Vienna
Title:	**Comprehensive elementary mode analysis of Mycoplasma mycoides JCVI-syn3.0.**		
Author keywords:	Enumeration of EFMs/EFVs, Method development, Reverse search, Properties of a minimal cell		
Abstract:	The enumeration of unique metabolic pathways in typical genome-scale metabolic models remains currently intractable. However, here we present a fresh take on this old problem: We report the complete enumeration of elementary flux modes (EFMs) in the genome-scale metabolic model of the synthetic cell, Mycoplasma mycoides JCVI-syn3.0. By making use of reverse search, we show that the EFM enumeration in metabolic networks is almost embarrassingly parallel, strongly scalable and requires negligible memory resources. In the case of JCVI-syn3.0, we find more than 4 billion elementary flux modes, indicating a surprising metabolic variability despite the cell's minimallity. Although a complete enumeration of EFMs in (large) genome-scale metabolic models remains out of reach, we show that at least the set of all (yield-)optimal EFMs can be enumerated. Thus, for the first time an unbiased analysis of alternate optima in flux-balance applications becomes possible in actual research practice.		

T25

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Atis	Elsts	Latvia	University of Latvia
Title:	**Automation of constrained kinetic metabolic model optimization by COPASI wrapper SpaceScanner**		
Author keywords:	Optimization, Kinetic model, Consensus, Stagnation, Software		
Abstract:	Different constraints can be introduced to improve biological feasibility of optimized kinetic models of biochemical pathways. Introduction of homeostatic constraint and total enzyme activity (called also amino acid pool) constraint lead to reduced solution space and longer optimization experiments. Several optimization methods fail to find feasible solutions while some others may enter stagnation. That requires more manual work to ensure reliable results, specially in case of exploring optimization potential of different combinations of parameters. COPASI wrapper SpaceScanner helps to automate execution of multiple parallel optimization runs by starting multiple identical COPASI optimizations. The tool is capable of automatic optimization termination when parallel runs have reached nearly identical (consensus) values and automatic change of the optimization method in case of stagnation or if no feasible solution is found. SpaceScanner can be configured to automatically analyse the space of all or user defined subsets of adjustable parameter combinations. This is useful for more advanced automation tasks, e.g. to rank the subsets according to their objective function value. Another application of this functionality is to determine the minimal subset of parameters that gives 'good enough' results according user-defined rules, e.g. that gives 80% of objective function growth compared to optimization of full set of adjustable parameters. SpaceScanner and interpretation of optimization results is demonstrated on examples with pathway scale kinetic models of yeast, sugar cane and Arabidopsis thaliana.		

T26

Philipp	Schneider	Germany	Max Planck Institute for Dynamics of Complex Technical Systems, Magdeburg, Germany
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Title:	**Characterizing and Ranking Computed Metabolic Engineering Strategies**		
Author keywords:	Computational strain design, Minimal Cut Sets, Constraint Based Metabolic Modeling		
Abstract:	The computation of metabolic intervention strategies from a mathematical model, is a key component of an integrated metabolic engineering approach. A broad range of methods has been developed for this task, including bilevel optimization routines and the framework of Minimal Cut Sets (MCSs). Some of them may return a large pool of possible intervention strategies from which the most suitable strategy must be selected. Here we present 10 criteria to characterize and rank a given pool of intervention strategies computed for growth-coupled product synthesis [1]. Some criteria are straightforward, for example, the number of interventions, the maximal growth rate and the guaranteed minimum product yield. Less intuitive are methods to assess the robustness of intervention strategies, e.g. with respect to loss of coupling or the undesired accumulation of metabolites. We also rank intervention strategies higher if they allow for higher thermodynamic driving forces or rely on flux re-routing in the central metabolism. Furthermore, strategies that have a significant overlap with alternative solutions are favored as they provide flexibility in implementation. We finally introduce the notion of equivalence classes for grouping intervention strategies with identical solution spaces. We demonstrate applicability of our approach by assessing minimal cut sets computed in a genome-scale model of E.coli for the growth-coupled synthesis of l-methionine and of the heterologous product 1,4-butanediol. We also give an outlook on extended methods to compute minimal cut sets making use of reaction insertions and substrate combinations [1] Schneider P., Klamt S. (2019) Bioinformatics, in press.		

T27

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Glenn	Hammond	United States	Sandia National Laboratories
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Title:	**Multiomics-based Metabolic Network Reconstruction and Pathway Analysis for Predictive Biogeochemical Modeling**		
Author keywords:	Metabolic network reconstruction, Multi-omics, FTICR-MS, Biogeochemical modeling, Elementary flux modes, Reactive transport modeling		
Abstract:	Multi-omics data have become increasingly available for environmental systems, however current biogeochemical models are not designed to effectively incorporate those molecular data. In this work, we use metabolic network reconstruction and metabolic pathway analysis as a tool to fill this gap. Metabolic network reconstruction is commonly used for modeling individual microorganisms, but their application to environmental microbiomes poses several challenges due to the complexity of the systems and the incompleteness of multi-omics data. We have developed a new biogeochemical modeling approach that overcomes these barriers, and here we demonstrate its effectiveness through a case study of two riverbank sediments with and without dense vegetation. Leveraging the US DOE's KBase (http://kbase.us/) modeling tools, we developed a new pipeline that enables network reconstruction from field metagenomes. Through a comparative pathway analysis of the two metabolic networks, we were able to identify biochemical reactions uniquely pertaining to each site, as well as those in common at two sites. Using the KBase chemoinformatics tools, we further incorporated high-resolution metabolite profiles from Fourier Transform Ion Cyclotron Resonance Mass Spectrometry (FTICR-MS) into metabolic networks. Finally, we formulated dynamic biogeochemical reaction models to integrate into a reactive transport model using the reaction sandbox of PFLOTRAN. For reproducible model development and simulations, we will publicly share the KBase narratives and Jupyter notebooks of in-house code to enable step-by-step implementation of the entire workflow. Our metagenome-based network building and pathway analysis can serve as a general modeling approach for studying other complex systems including human microbiota.		

T28

Katharina	Nöh	Germany	Forschungszentrum Jülich
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Title:	**A Critical View on Ockham's Razor as Criterion for Model Selection in Systems Biology**		
Author keywords:	Modelling, Model selection, Ockham's Razor, Bayesian Model Averaging, 13C Metabolic Flux Analysis		
Abstract:	Models have a fixed place in Systems Biology. They are logical machines, of different flavors and at different scales, for inferring quantities that cannot be obtained by direct observation and to aid our understanding of cellular systems. Here, the modeler is faced with a crucial trade-off: On the one side, models should be made comprehensive (or even as comprehensive as possible), to have the capacity to mimic the systems under study. On the other side, however, when too complex models are used for inference, the data is rendered uninformative due to the multitude of parameters involved. Model selection, guided by the principle of parsimony, offers data driven support and argues, from the viewpoint of probability theory, that simpler models are more likely to be true. However, when a vast number of model candidates exist, parsimonious model selection is not only technically difficult, but also questionable due to the high risk of false positives. Here, we investigate the consequences of parsimonious model selection by applying Ockham's Razor in the domain of 13C Metabolic Flux Analysis and explain the fundamental problem with parsimony as selection criterion: A single model candidate has not sufficient evidence to discard all the millions of remaining, possibly correct ones. In view of this, we argue that a more general approach is needed, which does not discard potential models, but instead estimates the uncertainty originating from the model formulation. By implementing Bayesian Model Averaging, we present a recipe for bypassing the reliance on a small sub-set of models.		

T29

Oliver	Hädicke	Germany	University of Applied Sciences Biberach
Title:	**In silico profiling of Escherichia coli and Saccharomyces cerevisiae as cannabinoid factories**		
Author keywords:	cannabinoid production, metabolic engineering, knockout strategies, Escherichia coli, Saccharomyces cerevisiae		
Abstract:	Cannabinoids are prenylated polyketides that are derived from fatty acid and terpenoid precursors. Heterologous microbial biosynthesis of clinically important cannabinoids is attracting more and more attention but so far, yields are still low. Two promising heterologous hosts are Escherichia coli and Saccharomyces cerevisiae, however a direct comparison of both hosts based on experimental data is not accessible. Therefore, by means of in silico analyses, the impact of the cannabinoid pathways of Cannabis sativa on the respective host's metabolism as well as the impact of different carbon sources were compared systematically. The focus was set on the yields of Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) as the main representatives of the highly diverse class of cannabinoids. Both hosts show limitations in energy and redox equivalents for high yield cannabinoid production leading to new overexpression strategies (heterologous enzymes/pathways) for an enhanced cannabinoid yield. Further, the choice of carbon source has a significant effect on cannabinoid yield. Metabolic engineering strategies for cannabigerolic acid, a general cannabinoid precursor, were identified which may further enhance product yields. Knockout strategies were identified using the approach of constrained minimal cut sets enforcing a coupling of growth to cannabinoid yields. This study provides for the first time a comprehensive and detailed in silico comparison of the most prominent heterologous hosts E. coli and S. cerevisiae as cannabinoid factories. The results provide valuable information for industrial-scale manufacturing of naturally occurring cannabinoids thus enabling the improvement of existing manufacturing platforms such as direct extraction from cannabis plants.		

T30

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Karl	Weitz	United States	Environmental Molecular Sciences Laboratory, Pacific Northwest National Laboratory
Robert	Young	United States	Environmental Molecular Sciences Laboratory, Pacific Northwest National Laboratory
Ganesh	Sriram	United States	Dept. of Chemical and Biomolecular Engineering, University of Maryland, College Park
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Title:	**Integrated Flux Analysis of Susceptible and Resistant Escherichia coli under Antibiotic Stress**		
Author keywords:	Metabolic flux analysis, Genome-scale, Antibiotic resistance, Transcriptomics		
Abstract:	The surge in antimicrobial resistance requires urgent development of innovative approaches to address the numerous resistant bacterial pathogen threats outlined by the CDC and WHO. Notably, a growing body of evidence suggests that the presumed fitness disadvantages of resistant pathogens conferred by expression of resistance genes is not fully accurate. Arising from these data is the increasingly attractive hypothesis that context-specific modification of metabolism is a key component of antibiotic resistance. Further exploration of the relationship between metabolism, antibiotic stress, and resistance is clearly needed. To address this gap in our fundamental understanding, we have compared the metabolic behaviors of wildtype and resistant strains of Escherichia coli through a combined transcriptomic and fluxomic analysis. Differential expression analysis identified significant shifts in activity in a diverse range of pathways between the WT and resistant strains as well as the resistant strains with and without antibiotic challenge. Furthermore, the resistant strains produced significantly more CO2 than the wildtype strain. Our preliminary findings suggest that the resistant strains reductively constrain their metabolism upon genomic and/or antibacterial stress. To elucidate the specific metabolic alterations, we are generating genome-scale flux predictions through the integration of transcriptomics data with MFA simulations. In our presentation, we will discuss the integrated flux predictions for each condition and explore the metabolic shifts that correspond to resistance and antibiotic stress. This study represents the first application of quantitative flux analysis to study resistant bacteria and should provide significant insight into the role of metabolic adaptation in antibiotic resistance.		

T31

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Title:	**Inferring optimal minimal media for genome-scale metabolic models using evolutionary algorithms**		
Author keywords:	Genome-scale metabolic models, Single organisms, Microbial communities, Optimization, Evolutionary Algorithms		
Abstract:	Genome-scale metabolic models (GSMMs) are valuable tools in metabolic systems biology for biomedical and industrial research and are becoming available for an increasing number of single organisms and, more recently, also for microbial communities. One of the most promising features for the use of GSMMs is the rational design of microorganisms in isolation or in communities that could turn them capable of producing desired compounds in industrially relevant amounts. The metabolic engineering or design problem can be simply formulated as the maximization of the production of a target compound by manipulating environmental conditions, performing genetic manipulations or even, in the case of a microbial community, manipulate the microbial composition in terms of species. In this work, an optimization framework has been implemented and validated that allows to find an optimal minimal medium composition for a given objective function, such as maximizing growth, or the production of a given target compound. This framework was fully implemented in Python language and the workflow of the optimization process uses Evolutionary Algorithms (EA). The code, installation files and documentation are available at the GitHub repository (https://github.com/BioSystemsUM/optimModels). For the validation of this framework, published GSMMs of single prokaryotic organisms and natural and synthetic microbial communities were used. All results were compared and validated with experimental data in literature. Overall, the results obtained for minimal medium composition using the developed tool showed biological significance, correctly predicting the minimal medium in aerobic/anerobic and light/dark conditions, as required by the specific organisms involved.		

T32 – Jāmaina pēc epasta

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Won Dong	Lee	Israel	Department of Biology, Technion
Elina	Aizenshtein	Israel	Department of Biology, Technion
Title:	**Inferring subcellular level metabolism with Compartmentalized Deconvoluted Metabolic Flux Analysis (Code-MFA)**		
Author keywords:	Subcellular compartmentalized flux analysis, Isotope tracing, Thermodynamic analysis,Cancer metabolism		
Abstract:	The inability to inspect metabolic activities within distinct subcellular compartments has been a major barrier to our understanding of eukaryotic cell metabolism. Numerous isozymes catalyze the same metabolic transformation in different compartment, having different flux, potentially in opposite directions – facilitating the shuttling of redox and energy co-factors across organelle membranes. The most direct approach for quantifying intracellular metabolic flux is isotope tracing coupled with computational Metabolic Flux Analysis (MFA). However, utilizing this approach with metabolic measurements performed on a whole-cell level typically limits its applicability to inferring whole-cell level metabolic flux – i.e. average flux through all subcellular organelles. Here, we developed a computational method for inferring cytosolic and mitochondrial specific metabolic fluxes based on whole-cell level measurements of metabolite isotopic labeling and concentrations. This is made possible by integrated modeling of compartment-specific isotope tracing as well as reaction and membrane transporter thermodynamics – where inferred Gibbs free energy of reactions in each compartment is associated with rates of isotope exchange (forward-to-backward flux ratio). While joint isotope tracing and reaction thermodynamics modelling is computationally hard, we provide an efficient iterative algorithm for inferring compartment-specific fluxes, concentrations, and reaction Gibbs free energy, as well as confidence intervals. We applied our method to several proliferating cancer cell lines, deriving a first comprehensive view of the interplay between mitochondrial versus cytosolic fluxes in central metabolism under physiological conditions. We expect this approach to be a highly useful tool for probing cytosolic and mitochondria metabolic dysfunction in cancer and other human diseases.		

T33

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Title:	**Probabilistic Integration of Flux Constraints and Thermodynamic Data in Metabolic Models**		
Author keywords:	Genome-Scale Models, Thermodynamics, Sampling		
Abstract:	Random sampling of the flux space can provide an unbiased description of the steady-state capabilities of a metabolic network. However, often unfeasible cycles and uncertainties in reaction directions lead to unrealistic predictions of flux distributions. We propose a probabilistic approach that combines estimates of Gibbs free energies with steady-state constraints to sample sets of reaction directions over the entire network using a modified MCMC method. By accounting for correlations in the estimation errors and for couplings between metabolite concentrations, we sample flux distributions consistent with thermodynamic constraints and uncertainties. We applied the method to models of E. coli growing on different carbon sources, specifically a reduced iML1515 model with ~700 reactions. For this network size, we successfully solved the resulting optimization problems for searching initial points, and we reached convergence of the sampler. We show that thermodynamics-based sampling, constrained by few physiological measurements, can accurately predict intracellular fluxes, as validated against 13C data. In addition, it yields predictions of intracellular metabolite concentrations. Intriguingly, we observe a common pattern in our results: in contrast to what a flux-only perspective of metabolism would suggest, the combination of flux and thermodynamic constraints results in multimodal posterior probability distributions of fluxes and metabolite concentrations. The emergence of multi-modal distributions therefore opens interesting new questions such as whether metabolic networks can indeed operate in different, discrete modes, while still displaying the same phenotype, and what the role of regulation in the selection of a specific mode would be.		

T34

Roland	Sauter	Norway	UiT The Arctic University of Norway
Ines	Heiland	Norway	UiT The Arctic University of Norway
Title:	**Estimating the Impact of Cofactor Concentration Changes in Genome-scale Models**		
Author keywords:	Genome-scale models, Constraint-based modeling, Cofactors, Cofactor concentrations, NAD		
Abstract:	Nicotinamide adenine dinucleotide (NAD) is the most common cofactor in human metabolism. Together with its phosphorylated form NADP, it is mainly recognized as a cofactor for redox reactions. As such it is reversibly interconverted between oxidized (NAD+) and reduced (NADH) states. It is less known as a substrate of NAD-consuming reactions involved in gene regulation and signal transduction, such as DNA repair or protein modification. NAD-consuming reactions lead to a rapid turnover of cellular NAD pools, with half-lifes as short as 15 minutes. Unless balanced by biosynthesis, cellular NAD concentrations decrease -- also a hallmark of age-related diseases. Yet, very little is known about the effects of altered NAD concentrations on whole cell metabolism. Creating computational models for such scenarios is challenging: Genome-scale constraint-based modeling techniques do currently not account for concentration changes of cofactors such as NAD. ODE-based techniques, on the other hand, can be used to describe dynamic concentration changes, but cannot easily be expanded to larger scales. We have therefore developed a method to estimate the effects of changed NAD concentrations in constraint-based models using Michaelis-Menten constants collected from databases such as Brenda and SabioRK. The pipeline developed for this approach automatically extracts these constants and scales the flux boundaries of NAD-dependent reactions accordingly. Using this approach we computed the effects of decreased NAD concentrations in published metabolic models, and compared the results to experimental data. We also analyzed the effects of altered NAD concentrations on the robustness of these models.		

T35

Johann	Rohwer	South Africa	Stellenbosch University
Carl	Christensen	South Africa	Stellenbosch University
Jan-Hendrik	Hofmeyr	South Africa	Stellenbosch University
Title:	**PySCeSToolbox: providing deeper insight into the regulatory behaviour of kinetic models**		
Author keywords:	Kinetic modeling, Metabolic control analysis, Generalised supply-demand analysis, Symbolic control analysis, Thermodynamic and kinetic regulation, Python		
Abstract:	High-level behaviour of metabolic systems results from the properties of, and interactions between, numerous molecular components. A more complete understanding of metabolic behaviour can be achieved by constructing and subsequently analysing kinetic models since these aim to capture all the relevant properties of the system components and their interactions. However, simulation of metabolic models, on its own, does not necessarily provide deeper insight and understanding. Here we present PySCeSToolbox, a collection of software tools that implement metabolic analysis frameworks to gain a more complete picture of metabolic system behaviour, control and regulation. PySCeSToolbox includes three main tools: RateChar, SymCA, and ThermoKin, which are computational implementations of generalised supply-demand analysis (GSDA), symbolic control analysis and a framework for investigating kinetic and thermodynamic contributions to enzyme regulation. GSDA can identify regulatory metabolites and trace routes of regulation in a metabolic network. This will be exemplified by analysis of kinetic models of aspartate-derived metabolism in Arabidopsis, and of pyruvate metabolism in Lactococcus lactis. Symbolic control analysis provides algebraic expressions for control coefficients in terms of elasticities and allows one to trace high level behaviour back to the properties of the low level components. We apply this method to above-mentioned pyruvate branch model in order to explain a previously observed negative flux response towards an increase in substrate concentration. Using the ThermoKin framework, we also quantify the contributions of enzyme binding and mass-action to enzyme elasticity separately, which allows for an even finer-grained understanding of flux control.		

T36

Sergio	Garcia	United States	University of Tennessee Knoxville
Cong	Trinh	United States	University of Tennessee Knoxville
Title:	**Solving the Modular Cell Biocatalyst Design Problem with Multi-objective Evolutionary Algorithms**		
Author keywords:	Modularity, Modular design, Modular cell, Multi-objective evolutionary algorithms, MOEAs		
Abstract:	A large space of chemicals with bulk and specialty applications could be industrially synthesized with genetically modified microorganisms. However, the current strain design process is prohibitively laborious and costly for broad industrial application of whole-cell biocatalysts. To tackle this challenge, modular cell design based on a chassis cell that can be combined with different product synthesis pathway modules has been recently proposed. The modular cell design problem was mathematically formulated using the framework of multi-objective optimization. This approach aims to minimize unexpected failure and avoids task repetition, leading to a more robust and faster strain design process. In this study, we evaluated a library of state-of-the-art multi-objective evolutionary algorithms (MOEAs) to identify the most effective method to solve the multi-objective modular strain design problem. Using the best MOEA, we found the effective design of highly compatible modular cells with many product synthesis modules. The best performing algorithm could provide better and more diverse design options that might help increase the likelihood of successful experimental implementation. We identified key parameter configurations to overcome the difficulty associated with multi-objective optimization problems with many objectives. Interestingly, we found that MOEA performance with a real application problem (i.e., modular strain design) does not correlate with artificial benchmarks. Overall, MOEAs provide powerful tools to tackle the modular cell biocatalyst design problem.		

T37

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Anne	Goelzer	France	INRA, UR1404, MaIAGE, Université Paris-Saclay, Jouy-en-Josas, France

Title:	**Automated creation of bacterial resource allocation models**
Author keywords:	Resource allocation, Resource Balance Analysis, RBApy, Software, Automated model generation, Bacteria, Escherichia coli
Abstract:	Resource Balance Analysis (RBA) is a constraint-based modeling paradigm suited for creation of whole cell models of bacteria in steady-state, and is based on the idea of parsimonious resource allocation between cellular processes. RBA models include descriptions of energy-relevant cellular processes such as metabolism, translation or protein folding, taking place within a limited cellular space. Model predictions include the growth rate, metabolic fluxes and concentrations of enzymes, transporters and molecular machines (ribosomes, chaperones). Due to such level of detail, these models require a lot of information additional to the metabolic reconstruction, such as protein localization and composition. This information is difficult to gather by hand and to incorporate into existing modeling formats. Here we present RBApy - a software that automates a great part of that work by accessing online databases for necessary information, builds a model in a flexible XML-based format, provides functions for model calibration, simulation and for interfacing to Escher maps and Proteomaps for visualization. RBApy models initially include translation and protein folding, but the format's flexibility allows for simple addition of cellular processes. In case suitable datasets (e.g. proteomics, fluxomics) are available, RBApy provides methods for model parameter estimation. The entire process of model creation, calibration and validation has been done in RBApy for Escherichia coli. RBApy makes whole-cell modelling and simulation accessible for a large diversity of prokaryotes. This should enable scientists to explore the predictive capacity of the parsimonious resource allocation principle on different bacteria and offer promising perspectives for synthetic biology applications.

T38

Christian	Lieven	Denmark	Novo Nordisk Foundation Center for Biosustainability
Moritz	Beber	Denmark	Novo Nordisk Foundation Center for Biosustainability
Nikolaus	Sonnenschein	Denmark	Novo Nordisk Foundation Center for Biosustainability
Title:	**Memote: A community-driven effort towards a standardized genome-scale metabolic model test suite**		
Author keywords:	Quality Control, Genome-scale metabolic models, Continuous Integration, Unit tests		
Abstract:	Genome-scale metabolic models (GEMs) are widely used in biotechnology and medicine. Yet, neither formal representation nor the functional requirements of GEMs are precisely defined. Without a consistent standard the comparability, reproducibility, and interoperability of models across groups and software tools cannot be guaranteed. Here, we present memote (https://github.com/opencobra/memote) an open-source software containing a community-maintained, standardized set of metabolic model tests, and its application to a large collection of published models. The tests cover a range of aspects from annotations to conceptual integrity and can be extended to include experimental datasets for automatic model validation. In addition to testing a finished model, memote can automatically test each increment when building a GEM. A comprehensive report displays the model's performance parameters, which supports informed model development and facilitates error detection. Memote provides a measure for model quality that is consistent across reconstruction platforms and analysis software and simplifies collaboration within the community by establishing workflows for publicly hosted and version controlled models.		

Abstracts for poster presentations

P1

Agris	Pentjuss	Latvia	University of Latvia
Uldis	Kalnenieks	Latvia	University of Latvia
Egils	Stalidzans	Latvia	University of Latvia
Janis	Liepins	Latvia	University of Latvia
Title:	**Stoichiometric modeling for novel engineering strategies of microbial folate production**		
Author keywords:	Zymomonas mobilis, Saccharomyces cerevisiae, Stoichiometric modeling, Metabolic engineering, FBA, FVA		
Abstract:	Vitamins are essential micronutrients that are needed in small quantities to properly maintain metabolism. Folate is one of the most important vitamins for metabolism. Folate insufficiency in human body is population scale problem in developing countries. Natural sources of folates are green vegetables, meat products, (especially liver), fermented milk products (cheese, yoghurt). However, due to cultural, regional, economical, health and other factors in many places of the world ,humans don't reach daily supply of folate (200 – 600ug) via diet. In the situation of current world population, it would make potential folic acid annual demand from 360 – 1440t. Currently folic acid is synthesized chemically, but interest to biotechnological process of folic acid is growing. Bifidobacterium spp. and Lactobacilli spp. Folate outcomes are not high (within 20–200ng / g DW). Overexpression of heterologous folate synthesis leads to increased yields (up to 2000ng / g DW). While the increase is considerable, it is rather small for sustainable industrial scale production purposes. We purpose to analyze potential of folate produyction in other microorganisms like Saccharomyces cerevisiae and Zymomona mobilis. Stoichiometric modeling can suggest optimal strategies for "wet lab" metabolic engineering and demonstrate which strategies to avoid. We applied genome scale stoichiometric model analyzes to find out folate production potential of S. cerevisae and Z. mobilis. In silico analyses shows, that folate yield can be as high as 40 mg/ 1 g glucose. Comparing to ug scale of previously published results, this demonstrates huge potential of folate production in biotechnological process.		

P2

Alexander	Smith	United Kingdom	University of Cambridge, GlaxoSmithKline
Alan	Robinson	United Kingdom	University of Cambridge
Title:	**Multi-tissue flux balance analysis of mitochondrial complex III inhibition**		
Author keywords:	Flux balance analysis, Mitochondrial metabolism, Multi-tissue modelling		
Abstract:	Mitochondria are organelles found in almost every eukaryote which are primarily responsible for generating chemical energy in the form of adenosine triphosphate (ATP). Mitochondrial dysfunction is linked to many late onset diseases such as Parkinson's, and inborn errors of mitochondrial metabolism cause severe neurological and physiological diseases. In addition, novel chemical entities being developed as drug leads are screened for cellular toxicity in which mitochondrial dysfunction is a major cause. However, due to the intricate network of pathways involved in metabolism, compounded by tissue specificity, there is a lack of knowledge about the specific metabolic adaptations caused by different types of mitochondrial dysfunction. This limits the accurate screening of mitochondrial dysfunction for pharmaceutical companies, thus preventing potentially useful drugs from being developed. Mitochondrial complex III is critical for oxidative phosphorylation, the main pathway for ATP generation, making it a primary cause of mitochondrial dysfunction. This study investigated complex III inhibition using a multi-tissue adaptation of the MitoCore model which consists of 324 reactions of mitochondrial metabolism. Tissue specific MitoCore models were generated for human heart, brain, liver and kidney using RNA-Seq data and combined into a single model. Geometric flux balance analysis was performed to investigate the adaptations that occur from liver complex III inhibition at varying levels. The simulations identified multiple pathway adaptations and biomarkers which can be utilized to identify the presence of complex III inhibition and an estimated inhibition level, results which are currently being experimentally verified.		

P3

Antonio	Rigueiro Mesejo	Germany	Heinrich Heine University, Düsseldorf, Germany
David	Heckmann	United States	University of California at San Diego, San Diego, USA
Esther	Sundermann	Germany	Heinrich Heine University, Düsseldorf, Germany
Martin	Lercher	Germany	Heinrich Heine University, Düsseldorf, Germany
Title:	**Explaining and extending the agronomical potential of CAM photosynthesis using computational models**		
Author keywords:	Photosynthesis, Crassulacean acid metabolism (CAM), Primary pathways, Plant metabolism, Central carbon metabolism, Agriculture, Production		
Abstract:	CAM (Crassulacean Acid Metabolism) is one of the three major photosynthetic pathways, characterized by stomatal closing during the day and carbon absorption during the night. Its main advantage is reduced transpiration, favored in very dry environments. However, field experiments have shown that CAM plants can have higher productivity and lower water requirements than current crops, making them a potential resource for genetic engineering. To understand the causes of the high CAM productivity and to quantify its limits, we developed a comprehensive in silico model that reproduces the metabolism and water economy of CAM plants. The model is based on a set of 30 differential equations and 45 physiological parameters. It describes from first principles the primary pathways of light harvesting, C3 and CAM photosynthesis, photosynthetic regulation, gas and water transport, leaf anatomy, and physical parameters such as light and temperature influencing the metabolic processes. We validated that the resulting simulations capture the observed plant physiology along day-night and seasonal cycles for different metabolic and anatomical configurations. The model explains how CAM plants reach very high productivities and predicts which plant parameters are required to achieve maximal efficiency. Our results explain the observed association between CAM and leaf succulence, and quantify the water saving potential of the pathway. Finally, the model reveals two potential targets that would facilitate the genetic engineering of more productive CAM crops and the introduction of CAM pathways in crops while keeping their current leaf anatomy.		

P4

Axel	von Kamp	Germany	Max Planck Institute for Dynamics of Complex Technical Systems
Oliver	Hädicke	Germany	University of Applied Sciences Biberach
Steffen	Klamt	Germany	Max Planck Institute for Dynamics of Complex Technical Systems
Title:	**Identification and analysis of metabolic pathways with maximal thermodynamic driving force**		
Author keywords:	Constraint-based modeling, Thermodynamics, CO2 fixation		
Abstract:	The directionality of a reaction flux in structural metabolic modeling is often constrained to be either forward or backward, when the physiological direction of the reaction is known, otherwise the reaction is considered to be reversible. When thermodynamics is considered, the net direction of a reaction is given by the sign of the Gibbs free energy change (negative sign for a forward flux). The Gibbs free energy change of a reaction can be calculated from its standard Gibbs free energy change and the metabolite concentrations. This standard Gibbs free energy change is usually unknown, but can be estimated via recently developed methods for the estimation of standard free Gibbs formation energies of the metabolites that participate in the reaction. Thereby, the integration of metabolite concentrations into structural metabolic modeling becomes possible, leading to applications like thermodynamic flux balance/variability analysis. Here, we take this approach one step further by presenting a mixed-integer linear program (MILP) which can be used to identify (shortest) thermodynamically feasible/optimal pathways in a given network and to analyze the thermodynamic limitations of such pathways. We apply our approach in an E. coli genome-scale model to systematically identify substrate-product combinations for which thermodynamically feasible pathways exist that assimilate CO2 into the product. Despite the fact that biomass synthesis cannot be coupled to net CO2 fixation in E. coli, 145 of the 949 cytosolic carbon metabolites allow for net CO2 incorporation along thermodynamically feasible pathways with glucose or glycerol as substrate.		

P5

Chaitra	Sarathy	Netherlands	Maastricht University
Martina	Kutmon	Netherlands	Maastricht University
Michael	Lenz	Germany	Johannes Gutenberg University Mainz
Michiel	Adriaens	Netherlands	Maastricht University
Chris T.	Evelo	Netherlands	Maastricht University
Ilja C. W.	Arts	Netherlands	Maastricht Centre for Systems Biology (MaCSBio)
Title:	**An integrative workflow to visualize Elementary Flux Modes in genome-scale metabolic models**		
Author keywords:	Elementary Flux Modes, Visualization, Data integration, Metabolic networks		
Abstract:	Elementary Flux Modes (EFMs) are an indispensable tool for constraint-based modelling and metabolic network analysis. However, systematic and automated visualization of EFMs, capable of integrating various data types is still a challenge. In this study, a semi-automated, customizable, MATLAB-based workflow was developed for graphically visualizing EFMs as a network of reactions, metabolites and genes. The workflow integrates COBRA and RAVEN toolboxes with the open-source tool, Cytoscape. Through a 4-step process, a genome-scale metabolic model was imported into MATLAB for EFM generation and analysis, followed by visualization and data mapping in Cytoscape. Once processed, the widely accepted SBGN layout was automatically applied, thus requiring minimal user effort in layout arrangement. Network manipulations in Cytoscape were semi-automated using R. The biological applicability of the workflow is demonstrated using EFMs generated from two genome-scale models, (1) iAF1260 (E. coli) and (2) Recon 2.2 (Human). Additionally, two different types of data, gene expression and reaction fluxes, were mapped onto the visualized EFMs. The workflow presented here marks an important step forward for EFM analysis. Utilizing the powerful, open-source Cytoscape platform not only allows network visualization and data mapping, but also opens new avenues for EFM extension with other molecular components. In summary, the features described above enable an integrated visualization in terms of both network components and data mapping, thereby contributing to comprehensive understanding of the processes described by the EFMs.		

P6

Cong	Trinh	United States	University of Tennessee Knoxville
Sergio	Garcia	United States	University of Tennessee Knoxville
Title:	**Design of modular cells by goal attainment optimization**		
Author keywords:	Modular cell, Modularity, Production modules, Goal optimization, Multiobjective optimization, Pareto optimality, Escherichia coli		
Abstract:	Goal attainment optimization is a mathematical framework to describe the simultaneous optimization of conflicting objectives that must all reach a performance above a threshold or goal. In this study, we use goal attainment optimization to design modular cells that can couple with various modules, where each goal corresponds to the minimum design requirements (i.e., yields and rates) of a target product. This modular design approach aims to overcome the prohibitively slow and difficult strain design process to enable a broader industrial application of whole-cell biocatalysis to produce fuels, chemicals, and therapeutics. Using a genome scale metabolic network model of Escherchia coli, we demonstrate that 20 biochemically diverse products can be effectively synthesized at high yields and rates by a modular cell with only a few genetic manipulations. Flux analysis reveals this broad modularity phenotype is supported by the natural modularity of core metabolic pathways. We envision this modular design framework can be applied for other synthetic biology applications such as design of modular bioremediation and biosensor cells.		

P7

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Kirstin	Gutekunst	Germany	Department of Biology, Botanical Institute, Christian-Albrecht-University, Kiel, Germany
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Title: **Metabolic network analysis of the unicellular cyanobacterium Synechocystis sp. PCC 6803 using 13C isotope experiments**

Author keywords: Cyanobacteria, Synechocystis, 13C metabolic flux analysis, GC-MS, NMR, Mixotrophic

Abstract:

A promising step towards eco-friendly processes in biotechnology is the use of carbon fixating microorganisms, which provide added-value products from a little more than sun light and carbon dioxide. The cyanobacterium Synechocystis sp. PCC 6803 appears capable to produce various biofuels and commodity chemicals, using photosynthesis (Chen et al. 2019). At present, major attributes of its metabolism remain hidden in the complex pathway network, which integrates routes for sugar breakdown and catabolism, the fixation of carbon dioxide, and the photosynthetic system (Chen et al. 2016). Here, we applied 13C metabolic flux analysis, which is the best measure to assess the metabolic phenotype of the photosynthetic bacterium (Kohlstedt and Wittmann, 2019). To address the complexity, we developed a strategy, which integrates labelling data from sugars and amino acids, obtained from GC-MS and NMR. The approach builds on a carefully optimized set-up for mixotrophic growth of Synechocystis sp. PCC 6803, which enables sufficient supply of light and oxygen during batch cultures. In addition to wild type, different mutants affected in central carbon metabolism, are studied.

Kohlstedt M, C Wittmann (2019) Metab. Eng. 54: 35.
Chen H, T Li, et al. (2019) Planta. 249: 195.
Chen X, K Schreiber, et al. (2016) Proc. Nat. Acad. Sci. USA 113: 5441.

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P8

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Santa	Prikule	Latvia	Institute of Microbiology and Biotechnology, University of Latvia
Elina	Didrihsone	Latvia	Latvian State Institute of Wood Chemistry
Juris	Vanags	Latvia	AS "Biotehniskais centrs"
Uldis	Kalnenieks	Latvia	Institute of Microbiology and Biotechnology, University of Latvia
Title:	**Crypthecodinium cohnii and Zymomonas mobilis syntrophy for production of omega 3 fatty acid**		
Author keywords:	Systems biotechnology, Syntrophy, Crypthecodinium cohnii, Zymomonas mobilis, Docosahexaenoic acid		
Abstract:	One of missions of industrial biotechnology is to produce valuable products from waste. In the current study we aim to establish a bioprocess of syntrophic co-cultivation of two microorganisms (Crypthecodinium cohnii and Zymomonas mobilis) at laboratory prototype level for bioconversion of renewables (molasses, the byproduct of sugar industry, and glycerol, byproduct of biodiesel production) into valuable vegetarian (produced by microorganisms) docosahexaenoic acid (DHA) from omega 3 fatty acid family. Cells of Z.mobilis strain (respiratory-deficient mutant derivative of the wild type strain Z.mobilis ATCC 29191) will be immobilized, following the previously described procedure of calcium alginate gel encapsulation. Mathematical modelling will be used for different components and at different stages of the syntrophic process to assist its improvement. The syntrophic bioprocess will be optimized with respect to (i) the medium composition, (ii) feed rates, (iii) oxygen supply, and (iv) the amounts of added immobilized Z. mobilis cells at particular stages of the fermentation. Genome and/or central carbon metabolism scale stoichiometric modelling and optimization will be performed to increase the utilization of cheap substrates and pre-treated residuals of C.cohnii. Bioprocess dynamics with respect to growth speed of batch fermentations will be modelled to ensure optimal proportions of syntrophic organisms, taking into account Z.mobilis production and immobilization as "slave" process of C.cohnii cultivation. Within several iterative cycles the fermentation data will be used for modelling and computer simulation of the bioprocess, and at the same time, the model-predicted dynamic behaviour of the system will aid further improvement of fermentation performance.		

P9

Elad	Noor	Switzerland	ETH
Moritz	Beber	Denmark	DTU Biosustain
Title:	**Web-based tools for metabolic pathway profiling**		
Author keywords:	Thermodynamics, Metabolic engineering, Metabolic pathway, Enzyme cost		
Abstract:	Our aim is to provide scientists with basic programming skills ways to analyze metabolic pathways using algorithms such as Max-min Driving Force and Enzyme Cost Minimization. The eQuilibrator website is a user-friendly interface for obtaining equilibrium constants and performing pathway analyses all through a simple online web interface. In addition, we provide a python package that can perform the same analyses, which is more suitable for large models and batch runs. These tools could be useful for metabolic engineers that need a way to compare alternative metabolic strategies in silico, as a filtering step before implementing them in vivo. In addition, pathway profiling can reveal evolutionary design principles and to predict the choice of a specific pathway in certain conditions.		

P10

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Jekaterina	Martynova	Latvia	University of Latvia, Institute of Microbiology and Biotechnology
Inese	Strazdina	Latvia	University of Latvia, Institute of Microbiology and Biotechnology
Zane	Lasa	Latvia	University of Latvia, Institute of Microbiology and Biotechnology
Nina	Galinina	Latvia	University of Latvia, Institute of Microbiology and Biotechnology
Reinis	Rutkis	Latvia	University of Latvia, Institute of Microbiology and Biotechnology
Uldis	Kalnenieks	Latvia	University of Latvia, Institute of Microbiology and Biotechnology
Title:	**Transfer of acetaldehyde synthesis outside the cytoplasm: a novel path towards improving the acetaldehyde production and tolerance in Zymomonas mobilis**		
Author keywords:	Biotechnology, Zymomonas mobilis, Acetaldehyde		
Abstract:	Acetaldehyde is an organic compound with wide application in the chemical industry. In the ethanologenic bacterium Zymomonas mobilis it is generated by cytoplasmic pyruvate decarboxylase (PDC) reaction. It' s accumulation occurs when culture is cultivated aerobically, due to withdrawal of NADH from the alcohol dehydrogenase reaction by respiration. Acetaldehyde accumulation in cell cytosol inhibits cell growth and metabolism. In the present study our aim was to construct fusions of PDC with the signal sequences of periplasmic enzyme gluconolactonase, to relocate acetaldehyde generation from cell cytosol to the periplasmic compartment. Zymomonas mobilis strains Zm6 (ATCC29191) and a strain with an pdc-deficient background (strain Zm6-pdc, derived from Zm6) Zm6-pdc were transformed by electroporation with plasmid pBBR1MCS2 containing fusion of the signal sequence of the periplasmic enzyme gluconolactonase and ORF of pdc gene under glyceraldehyde-3-phosphate dehydrogenase promoter (Pgap). Both mutants and their respective parent strains were cultivated under aerobic conditions. Growth, product synthesis and PDC activity in cytosolic and membrane fractions were monitored. It was shown that the plasmid construct, carrying pdc with the periplasmic signal sequence, expressed an active pyruvate decarboxylase, which was partly localized outside the cytosolic fraction. Zm6-pdc, complemented with this construct, restored its PDC activity, and switched from aerobic accumulation of pyruvate to acetaldehyde synthesis.		

P11

Eleni	Vasilakou	Netherlands	Delft University of Technology
Mark C.M.	van Loosdrecht	Netherlands	Delft University of Technology
Aljoscha	Wahl	Netherlands	Delft University of Technology
Title:	**Escherichia coli metabolism under short-term repetitive substrate dynamics: Adaptation and trade-offs**		
Author keywords:	Escherichia coli, Feast-famine regime, Substrate dynamics, Dynamic metabolic responses, Energy homeostasis		
Abstract:	Microbial metabolism is highly dependent on the environmental conditions. Especially, in large-scale bioreactors, microorganisms encounter dynamic conditions, due to mixing limitations, which influence their performance. Many attempts have been made to study their behaviour in lab-scale by means of single-stimulus experiments, which cannot, however, recreate the repetitiveness of these dynamics present in an industrial fermentation. In this study we applied a feast-famine regime in an aerobic Escherichia coli culture by varying the substrate availability in a time-scale of seconds. These perturbations were applied in long-term repetitive cycles, allowing cells to adapt and enabling the study of their physiology and metabolic response. We observed an increase of the substrate and oxygen consumption (average) rates during the feast-famine, compared to a steady-state (chemostat) reference environment, verifying the adaptation of the microorganism to the dynamic environment. Under these dynamic conditions, the biomass yield dropped significantly (17.3%), likely as a trade-off for survival and adaptation. E.coli rapidly increased its uptake rate within 10 seconds after the beginning of the feeding, leading to the subsequent accumulation of intracellular metabolites. Depletion of the pools followed during the famine phase. Remarkably, the energy charge of the cells remained unaffected under these dynamic conditions, suggesting a strong regulation. In this work we were able to provide reproducible experimental data, indicating how the metabolic responses of Escherichia coli are regulated under repetitive substrate dynamics. In addition, we showed the importance of losses in biomass yield, which can have a significant impact on the productivity of large-scale industrial bioprocesses.		

P12

Elzbieta	Al-Saidi	United Kingdom	Oxford Brookes University
Mark	Poolman	United Kingdom	Oxford Brookes University
Isabel	Bermudez	United Kingdom	Oxford Brookes University
Yaroslav	Nartsissov	Russia	Institute of Cytochemistry and Molecular Pharmacology
Title:	**Computational modelling of glycine metabolism in the CNS**		
Author keywords:	Glycine metabolism, Neuron metabolism, Structural model		
Abstract:	Glycine is the second major inhibitory neurotransmitter in the CNS and its primary target is the Cl- ion selective glycine receptor (GlyR). Expression of GlyR is highest in the brain stem and spinal cord where glycinergic inhibition regulates smooth and skeletal muscle movements, peripheral sensory stimuli, and others. Availability of dischargeable glycine in the presynaptic neuron regulates glycinergic signalling and thus its concentration homeostasis is necessary. This is demonstrated via occurrence of rare encephalopathies resulting from its disruption. It is thought that glycine does not readily pass the blood-brain barrier and so the majority of it is synthesised in vivo, mostly from serine through serine hydroxymethyltransferase (SHMT) catalysis. Available neurotransmitter is shuttled between glial cells and neurons through its vesicular release and uptake by the glycine transporter proteins (GlyT1, GlyT2), and the alanine-serine-cysteine transporter (Asc-1). In addition, SHMT-mediated serine- glycine interconversion feeds carbon units into the one-carbon metabolism responsible for the synthesis of cell macromolecules. Following, it has been proposed that this pathway may be implicated in cancer cell proliferation. Given the importance of glycine homeostasis in neuronal signalling, as well as its potential involvement in brain cancer formation, we are developing a structural model of glycine metabolism in a neuron. The model is derived from the generic human metabolic reconstruction, Recon 2, pruned to a cell-specific model using published transcriptomic data. The model will be used to gain insight into glycine synthesis and degradation pathways in the mammalian brain.		

P13

Giulia	Slaviero	Germany	Max Planck Institute for Dynamics of Complex Technical Systems
Steffen	Klamt	Germany	Max Planck Institute for Dynamics of Complex Technical Systems
Title:	**Construction of a kinetic model of the central carbon metabolism in E. coli describing the switch from aerobic to anaerobic growth**		
Author keywords:	Escherichia coli, Kinetic modeling, Metabolic engineering, Fermentation		
Abstract:	Escherichia coli is one of the most important model organisms and workhorses for biotechnological applications. In recent years, the use of mathematical models, especially of constraint-based metabolic models, helped getting a better understanding of its metabolism and also provided a basis for the computational design of production strains. However, inherent quantitative relationships and the transient behavior of E. coli's metabolism can only be understood with dynamic models. However, despite the rapidly growing amount of experimental data, still, only a very limited number of kinetic models of the central metabolism of E. coli can be found in the literature. This work seeks to improve an existing model [1] with the goal to simulate E. coli's metabolism under changing oxygen concentrations and to predict changes when intervening in its energy and central metabolism. We needed to introduce several modifications in the model including (1) a growth rate law that considers stoichiometric requirements of the precursors, (2) introduction of co-factors, such as ATP, ADP, NADP(H) as explicit metabolites, and (3) proton translocation and ATP synthesis in the electron transport chain. The derived model is validated using experimental data and shows a more robust behavior and improved predictive capabilities compared to the original model. We discuss different application examples including, for example, (1) the predicted behavior of strains with a targeted increase of cellular ATP turnover, and (2) the reorganization of metabolic fluxes when switching from aerobic to anaerobic production. [1] Matsuoka et al. (2017) Biotechnol Biofuels, 10:183.		

P14

Helena	Herrmann	United Kingdom	The University of Manchester
Jean-Marc	Schwartz	United Kingdom	The University of Manchester
Giles	Johnson	United Kingdom	The University of Manchester
Title:	**Using metabolic modelling to understand the limitations to photosynthesis under changing environmental conditions**		
Author keywords:	Metabolic modeling, Primary metabolism, Plant biology		
Abstract:	As the global climate changes through this century, there will be a need to shift plant growth to times of the year when temperatures are suboptimal and more variable. In order to breed plants for a shifted growth season, we need to understand the limits on photosynthesis across different environmental conditions. We use both kinetic and constraint-based modelling techniques in order to understand the metabolic changes required for photosynthetic acclimation to changing environmental conditions. Using modelling and experimental data from six different temperature conditions, we identify metabolic changes required for photosynthetic acclimation of Arabidopsis thaliana across its physiological temperature range. Pioneering the use of flux sampling for studying network flexibility in wild-type and mutant plants, we identify necessary metabolic changes required for cold acclimation. Using dynamic modelling we predict which of the reactions linking photosynthetic uptake to leaf carbon storage and export are most temperature sensitive.		

P15

Hugo	Dourado	Germany	Heinrich-Heine Universität
Martin	Lercher	Germany	University of Düsseldorf
Title:	**An Analytical Theory of Cellular Growth**		
Author keywords:	Balanced Growth, Elementary Flux Modes, Growth Optimization, Cellular costs and benefits		
Abstract:	The biological fitness of unicellular organisms in constant environments is given by their balanced growth rate, i.e., by the rate with which they replicate their biomass composition. Evolutionary optimization of this growth rate occurred under a set of physicochemical constraints, including mass conservation, reaction kinetics, and limits on dry mass per volume (cellular capacity). Mathematical models that account explicitly for these constraints are inevitably nonlinear, and their optimization has been restricted to small, non-realistic cell models. States of maximal balanced growth are elementary flux modes. Here, we provide explicit expressions for individual protein concentrations, fluxes, and growth rate in a given elementary flux mode of an arbitrarily sized balanced growth model (BGM), all of which are uniquely determined by the concentration vector (total protein and metabolites). We provide explicit and intuitively interpretable expressions for the marginal fitness costs and benefits of individual concentrations. At maximal balanced growth, the marginal net benefits of each metabolite concentration and of total protein concentration equal the marginal benefit of the cellular capacity. Based solely on physicochemical constraints, our work unveils fundamental quantitative principles of balanced cellular growth, quantifies the effect of cellular capacity on fitness, and leads to experimentally testable predictions.		

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Title:	**iHD75321 – towards the metabolic model of the Quercus suber (Cork Oak Tree)**
Author keywords:	GSM model, Cork, Quercus suber, Metabolic network, Merlin
Abstract:	The cork oak tree, Quercus suber, is an important renewable resource from which wine stoppers and many other natural products are derived. It is important to have a better understanding of the genomics and metabolomics of the tree to obtain high quality cork. In this work we present a metabolic genome-scale model for Quercus suber, validated for the leaf. We used merlin (www.merlin-sysbio.org) to reconstruct the draft metabolic model. The enzymes were annotated using BLAST against SwissProt and TrEMBL. The central carbon metabolic pathways were checked manually. The biochemical reactions mass balance, as well as the blocked reactions were verified and corrected. The biomass composition was determined in terms of proteins, carbohydrates, lipids, cofactors, DNA and RNA components using approaches similar to previous plant models such as AraGEM and Tomato. The required drains for photons, inorganic compounds CO2, H2O, O2 and sources of Nitrogen, Phosphate and Sulphur are defined to simulate intake/secretions. The obtained Cork draft model consists of 3269 reactions, 2934 metabolites and 7531 genes of which 405 are transporters. Using Flux Balance Analysis, non-zero flux was observed in 1200 reactions. This model has been checked for biomass production using simulation tools such as Optflux [9]. The model is able to simulate both photosynthetic (light) and respiration (dark) reactions. To the best of our knowledge, this is the first metabolic model of a tree species. We believe that this model will bring new insights for Quercus suber studies such as the formation process of cork and plant metabolic modeling.

P18

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Title:	**Elucidation of dynamic metabolic regulation and exploration of toxic pathway intermediates as antifungal drug targets**
Author keywords:	Pathway regulation, Dynamic optimization, Toxic intermediates, Pathogenic fungi, Glyoxylate shunt
Abstract:	In recent years many characteristics determining the time optimal regulation of metabolic pathways were studied by dynamic optimization. Among these a key finding of our work was that toxic intermediates influence the position of highly regulated enzymes and guide us to valuable antimicrobial targets. We propose a disturbance of the optimal regulation as an antimicrobial strategy to provoke an endogenous accumulation of a toxic intermediate.Among pathogenic microbes, fungal species are an underestimated threat to human health and difficult to treat due to a small number of antifungal drugs. Since the virulence of fungi relies heavily on their metabolic versatility, we decided to explore the landscape of toxic intermediates and drug targets in the metabolic networks of pathogenic fungi. In order to do this, we employed machine learning to create a new toxicity prediction tool for fungi. The identification of drug targets is supported by the integration of toxicity prediction with metabolic networks from the KEGG database as well as estimates of enzyme regulation. With these resources, which will be available as a web service, we analyzed fungal specific pathways for toxic intermediates. As a key result we could identify the toxic intermediate glyoxylate as target for accumulation in the pathogen Candida albicans. The intermediate is part of the glyoxylate shunt which is a virulence factor of C. albicans to survive in the glucose poor phagolysosome of host macrophages. Interestingly, experimental investigation shows that C. albicans relies on multiple enzymes which control glyoxylate accumulation providing new targets for antifungal drugs.

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Igor	Grigoriev	United States	lawrence berkeley national laboratory
Christopher	Henry	United States	Argonne National Laboratory
Title:	**Fungal Modeling in KBase: Automated Reconstruction, Evaluation and Comparison of Diverse Genome-Scale Fungal Metabolic Models**		
Author keywords:	Fungal, Modeling, Build, Model, Automated, reconstruction, metabolic, KBase, MycoCosm		
Abstract:	Genome-scale fungal metabolic models are an efficient way of predicting phenotypes across various environmental conditions. These metabolic models are a key tool in understanding fungal-bacterial and plant-fungal community behavior. However, automating the construction of predictive fungal models has been a challenge. Here we introduce a methodology to construct genome-scale fungal models in an automated fashion based on a curated set of reactions that are derived from 14 published fungal models and KEGG ontologies. As the basis for the method, we produced a fungal model template that encompasses the biochemistry data from the published fungal models and the structural annotations from the associated fungal genomes. Our approach uses structural annotations of any user-submitted fungal genome and computes a set of orthologous proteins against the curated fungal template in order to assert the presence or absence of specific biochemical reactions and pathways. Once the orthologous protein families are determined, the related biochemistry data is propagated to construct a new draft metabolic model. This method is deployed in the Department of Energy Systems Biology Knowledgebase (KBase). (https://narrative.kbase.us/) as an app called "Build Fungal Model". This method is able to produce a draft fungal metabolic model in one hour. We applied this new app to construct draft fungal models (available via KBase). for more than 130 fungal genomes imported from the Joint Genome Institute (JGI) MycoCosm resource (https://genome.jgi.doe.gov/programs/fungi/index.jsf). We compared these models side-by-side, exploring how each genome overlaps with our curated model template and plotting model variance along the phylogenetic tree of fungal genomes.		

P20

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Title:	**Personalized parametrization of metformin pharmacokinetics taking into account genetic variance**		
Author keywords:	Personalized model, Pharmacogenetic, Metformin, Mathematical modeling, Type 2 Diabetis		
Abstract:	Metformin hydrochloride belongs to the peroral antidiabetic drug class of biguanides and improves glucose tolerance in patients with T2D, lowering both basal and postprandial plasma glucose by reduction of hepatic neogenesis in non-insulin-dependent diabetes mellitus patients. Despite wide prescription of metformin, critical information about its precise personalised dosing, which is very important due to large variability of interindividual pharmacokinetics, is still unknown. It has been previously found, that metformin therapy is inefficient up to 1/3 of patients in the first year of the therapy. The efficiency of therapy is depended on metformin concentration in particular patient after administration, which could be therapeutic, subtherapeutic or supratherapeutic, or might even result in metformin accumulation in the body. The intraindividual response to metformin therapy could be due to pharmacogenetic reasons. The variance of coding genes for OCT1, OCTN1, OCT2, OCT3, MATE1 and MATE2 transport proteins could have high impact on pharmacokinetic parameters with genetic variability. Personalised model takes into account several individual characteristics of person -as weight, time-series of metformin concentration in blood, erythrocytes and urine for single metformin dose and genetic information to ensure safety and efficacy of the metformin therapy. Having time-series of metformin concentration dynamics in different tissues and body fluids and particular patient pharmacogenetic data, we have sufficient competence to parameterize the model of healthy human case using software COPASI. The general model of metformin pharmacokinetics is built as a system of ordinary differential equations (ODE) that describes the transport of administered metformin through tissues and body fluids.		

P21

Jennifer	Chase	United States	Northwest Nazarene University
Title:	**Flux control analysis of glycolysis in uterine cells with a COPASI kinetic model**		
Author keywords:	Glycolysis, COPASI, Kinetics, Metabolism		
Abstract:	The cells lining the uterus secrete a carbohydrate-rich metabolite broth containing lactate, pyruvate and glucose to support early embryo development. Changes in the levels of hormones, including estrogen (E2) and progesterone (P4), must shift the metabolism of these cells during the uterine cycle from storage of glycogen to releasing of glucose and glycolytic products to the uterine lumen. Because most mammalian embryos are lost in this early stage, there is a critical need to understand how the nutrient supplies are regulated. We have characterized the system in mink uterine epithelial cells (GMMe) and have revised a kinetic model of HeLa metabolism to identify crucial controlling steps. GMMe cells were treated with P4, E2, or vehicle. Glycogen, glycolytic flux, enzyme Vmax and Kms, and steady-state metabolite levels were measured spectrophotometrically using standard coupled reactions in lysed cells. Glucose uptake and oxygen consumption were measured using assay kits. The kinetic model was constructed in COPASI 4.25 and unknown parameters were fit to the fluxes or used HeLa values. Glycolytic flux and glucose uptake was unchanged by hormone treatment. However, E2 treatment downregulated the Vmax of 9 enzymes, while P4 only affected some Kms. MCA implicated the pentose phosphate pathway, hexokinase, and phosphofructokinases as substantially flux controlling for glycolysis. E2 appears to act not to affect glycolysis but rather to increase the levels of the metabolites which need to be released for the embryo nutrition. This model enables identification of risk factors as therapeutic targets for fertility in mink and other mammals.		

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Title:	**Metabolite Accumulation under Dialysis – Competition and Clearance**		
Author keywords:	Kinetic modeling, Dialysis, Hemodialysis, Clearance of uremic toxins, Albumin, tryptophan, indoxyl sulfate		
Abstract:	Hemodialysis remains the therapeutic mainstay for patients with advanced chronic kidney disease. But even with recent advances, the efficacy of dialysis to clear toxic protein-bound, uremic solutes remains far below the filtration capacity of a healthy kidney. In blood, many of these toxins compete for the binding sites of serum albumin with native, small organic molecules including essential metabolites. We hypothesized that the toxin levels and their affinity to albumin affect free metabolite levels in blood. In order to analyze this dynamic interrelationship, we constructed a kinetic, multi-compartment model of metabolites and toxins. We focused on the essential amino acid tryptophan, its metabolites, and indoxyl sulfate, a highly thrombogenic uremic solute found to accumulate in the blood of patients with chronic kidney disease. Using measured binding affinities and simulating repeated rounds of dialysis, according to current practice, we were able to simulate the observed accumulation of indoxyl sulfate in dialysis patients. This accumulation increases the portion of unbound tryptophan, causing a drain of native metabolites during dialysis and altered amino acid metabolism. The latter was simulated by combining our hemodialysis model with a previously published model of human tryptophan metabolism. Our model serves as a prototype demonstrating the competition of different metabolites, including microbiota derived toxins, such as indoxyl sulfate, for binding and transport in blood and across biological membranes. This brings us closer to whole-body metabolic models and may provide insight into the long-known link between chronic kidney disease and metabolic diseases, such as obesity and diabetes.		

P23

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Title:	**FlySilico: Flux balance modeling of Drosophila larval growth and resource allocation**		
Author keywords:	Drosophila melanogaster, holidic medium, metabolic profiling, growth control, flux balance modeling, FBA, constraint-based model		
Abstract:	Organisms depend on a highly connected and regulated network of biochemical reactions fueling life sustaining and growth promoting functions. While details of this metabolic network are well established, knowledge of the superordinate regulatory design principles is limited. Here, we investigated by iterative wet lab and modeling experiments the resource allocation process during the larval development of Drosophila melanogaster. We chose this system, as survival of the animals depends on the successful allocation of their available resources to the conflicting processes of growth and storage metabolite deposition. First, we generated “FlySilico”, a curated metabolic network of Drosophila, and performed time-resolved growth and metabolite measurements with larvae raised on a holidic diet. Subsequently, we performed flux balance analysis simulations and tested the predictive power of our model by simulating the impact of diet alterations on growth and metabolism. Our predictions correctly identified the essential amino acids as growth limiting factor, and metabolic flux differences in agreement with our experimental data. Thus, we present a framework to study important questions of resource allocation in a multicellular organism including process priorization and optimality principles.		

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Title:	**Dynamic metabolism of trehalose and its role in glucose recycling in Saccharomyces cerevisiae using 13C-labeling**		
Author keywords:	Trehalose metabolism, Dynamic fluxes, 13C labeling, Yeast, Storage carbohydrates, Glucose recycle		
Abstract:	At low growth rates Saccharomyces cerevisiae accumulates high amounts of trehalose, a storage compound produced from glucose, for two purposes: energy and carbon storage, and stabilization during stress conditions. Trehalose can be converted into glucose through enzymatic hydrolysis catalyzed by either Nth1p/Nth2p or Ath1p. To investigate the role of trehalose in glucose recycling in yeast, we grew a mutant strain lacking trehalase activity under dynamic feast/famine conditions and compared its metabolism to that of a wild-type strain. We found that a major contribution to glucose recycle is mediated by Ath1p, an enzyme catalyzing the extracellular degradation of trehalose. This mechanism largely explains observations during 13C-labeling experiments where extracellular glucose labeling decreases in time, indicating another source of glucose. Main differences were found in CO2 and O2 rates with values about 10% lower in mutant strains, while qTreh was up to 9-fold higher. The extracellular trehalose concentration increased up to 10-fold in cultivations with mutant strains. During the feast/famine, the extracellular glucose concentration was 60% lower in the mutant strain, while the extracellular trehalose was 24-fold higher. Likewise, the intracellular trehalose was about 2-fold higher than in wild-type strain, while intracellular glucose decreased about 8-fold. The mutant strain also showed lower ATP concentration decreasing the energy charge when glucose availability was low. Flux estimations suggest a 20% higher glucose uptake in the wild-type, which is most likely due to extracellular glucose recycle. The present work comprehensively presents the role of trehalose metabolism in yeast from a quantitative point of view.		

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Title:	**Model-based optimisation of phenol consumption by yeast Rhodotorula glutinis**		
Author keywords:	Genome scale metabolic model, Rhodoturula glutinis, Optimization, Phenol degradation		
Abstract:	Olive mill wastewater (OMW) is a significant by-product of the food industry of the olive oil producer countries in Mediterranean basin with a high environmental impact, when not appropriately treated. However, at the same time OMW is rich in organic compounds, which can either be used directly after extraction, or valorized via biocatalytic processes. Many studies have been performed by industrial and research organizations in order to remediate OMW, which has detrimental effects on environment due to its high phytotoxicity caused by the presence of polyphenol content with low biodegradability. Project RHODOLIVE concentrates on development of a sustainable bioprocess for OMW bioremediation concentrating on phenols (hydroxytyrosol, tyrosol, coumarate and others) with Rhodotorula glutinis in order to produce high value-added bioproducts; carotenoids (with specific focus on βcarotene, thorularhodin), bioactive phenolic compounds (with specific focus on luteolin), biolipids, and total biomass. A genome scale stoichiometric model is developed to assess the potential of R. glutinis in OMW bioremediation and simultaneous production of high value bioproducts. Model-based metabolic engineering of R. glutinis is performed assessing bioremediation potential by removing and adding particular reactions or pathways.		

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Title:	**Predicting Nutritional Uptakes of Bacillus subtilis by Integrating Gene Expression Profiles into Constrained-Based Metabolic Models**		
Author keywords:	Flux balance analysis, Gene expression profiles, Metabolic network modeling, Mixed-integer linear programming, Thermodynamically infeasible loops		
Abstract:	Finding drug targets for antimicrobial treatment is a central focus in biomedical research. To discover new drug targets, we are interested in finding out which nutritional needs are essential for pathogenic microorganisms in the host or under specific circumstances. Besides this, metabolic fluxes have been successfully constructed and predicted by employing flux balance analysis (FBA) based on constrained based modeling. We develop FBA models using the stoichiometric knowledge of the metabolic reactions of a cell and combine this with experimental data, particularly gene expression profiles. We aim to identify essential drug targets for specific nutritional uptakes of pathogenic microorganisms. As a case study, we implemented our method by applying data of B. subtilis grown on eight different carbon sources. We used a metabolic model, gene expression data, and metabolic flux data from 13C tracing experiments for validation. We linearly mapped the expression values of the enzyme coding genes to the corresponding predicted fluxes by solving an optimization problem based on mixed-integer linear programming (MILP). A new method was developed to reduce thermodynamically infeasible loops (RED-TIL) to improve prediction results. Validation was performed by comparing predicted flux values with the fluxes from the 13C labeling experiments of the same conditions, and of another, independent dataset. By employing our method, our trained model could correctly identify the major carbon sources. Besides, our new method, RED-TIL, is faster compared to existing methods.		

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Title:	**Flux balance analysis and other constraint-based methods fail to pre-dict the effects of non-lethal metabolic gene knockouts in E. coli and yeast**		
Author keywords:	FBA, Constraint-based analysis, Gene knockouts		
Abstract:	Flux balance analysis (FBA) and related constraint-based methods have been shown to predict gene essentiality with high accuracy. However, it is not clear how reliably they predict mutant physiology for non-essential gene knockouts, as systematic analyses that apply the different constraint-based methods proposed for this problem to genome-scale data for multiple organisms are lacking. Here, we apply FBA and its popular extensions, including methods specifically developed for non-essential gene knockout predictions (MOMA, ROOM) and methods accounting for macro-molecular crowding (MOMENT, ccFBA), to data on non-essential gene knockout effects in E. coli and Saccharomyces cerevisiae. For a given metabolic model, simulation method, and environment, we find that predicted biomass fluxes across gene knockouts are restricted to a small number of distinct values. In each case analyzed, predictions explain only a small fraction of the observed variance in growth rate, fitness, or biomass yield. Even in the best cases, model-based predictions lead to coefficients of determination that are barely better than those of a trivial “model” assuming identical fitness for all knockouts. The constraint-based models perform slightly better when attempting to classify non-essential gene knockouts into those with and without fitness effects. However, even the best-performing methods – linear and quadratic MOMA – predict only between 20% and 40% of experimentally observed deleterious fitness effects. We speculate that knockouts cause metabolite concentration changes that initiate misguided regulatory responses, which are impossible to predict by optimization-based methods agnostic of regulatory interactions.		

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Title:	**Extensions to the sybil R package for constraint-based analyses: FBA with molecular crowding and efficient removal of thermodynamically infeasible loops**
Author keywords:	ccFBA, Constrained-based modeling, FBA, Flux variability analysis, Flux-balance analyses, GNU R, MOMA, MOMENT, ROOM, Sybil, sybilccFBA, sybilcycleFreeFlux, Thermodynamically infeasible loops
Abstract:	sybil (Gelius-Dietrich et al. 2014) is an open source software package for efficient constraint-based modelling in R. sybil provides methods such as flux balance analysis (FBA), minimization of metabolic adjustment (MOMA), and minimization of regulatory off/on modification (ROOM). sybil is optimized for large-scale simulations and can evaluate the effects of whole-genome single gene deletions on complete bacterial metabolic models faster than comparable programs. With its highly efficient APIs for a variety of widely used solvers (GLPK, CPLEX, COIN-OR Clp, and Gurobi), SyBiL provides a high amount of flexibility to fit user requirements. Here, we present two recent extensions to sybil. (1.) The extension package sybilccFBA allows FBA analyses that account for molecular crowding. sybilccFBA provides an improved general implementation of MetabOlic Modeling with Enzyme kineTics (MOMENT), as well as an implementation of the original MOMENT algorithm (Adadi et al. 2012). ccFBA uses enzyme kinetic data and molecular weights to constrain FBA calculations, accounting for multi-functional enzymes. It comes with fully parameterized models for Escherichia coli and Saccharomyces cerevisiae. (2.) Predictions from constrained-based metabolic modeling methods such as FBA and flux variability analyses frequently include thermodynamically infeasible loops (internal cycles). The extension package sybilcycleFreeFlux (Desouki et al. 2015) provides implementations that remove such infeasible loops by postprocessing solutions obtained by constraint-based metabolic modeling methods (Müller & Bockmayr 2013). Müller 2013 https://academic.oup.com/bioinformatics/article/29/7/903/253327 Adadi 2012 https://doi.org/10.1371/journal.pcbi.1002575 Gelius-Dietrich 2014 https://doi.org/10.1186/1752-0509-7-125 Desouki 2015 https://doi.org/10.1093/bioinformatics/btv096

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Title:	**Metabolic cross-talk between human dendritic cells and fungal pathogen Aspergillus fumigatus reveals the modulation of metabolic strategy of both the host and pathogen**		
Author keywords:	Metabolic modeling, Elementary mode analysis, Aspergillus fumigatus, Dendritic cells		
Abstract:	Aspergillus fumigatus is an airborne fungal pathogen which can cause a hypersensitive reaction, mucosal colonization and even life-threatening invasive infections in the immune-compromised host. The conflict against regulated immune responses of human dendritic cells (DCs) is one of the vital processes for survival of A. fumigatus during infection. Therefore, the study of metabolism defining infection elucidates the survival strategies of pathogen and responses of the organism. We established a metabolic model of A. fumigatus central metabolism during infection of DCs and calculated the metabolic pathway (elementary modes; EMs). Transcriptome data were used to identify pathways activated when A. fumigatus is challenged with DCs. For both A. fumigatus and DCs, we outlined specific metabolic changes in response to that confrontation. In particular, amino acid metabolic pathways, alternative carbon metabolic pathways and stress regulating enzymes were found to be active. Metabolic flux modeling identified further active enzymes such as alcohol dehydrogenase, inositol oxygenase and GTP cyclohydrolase participating in different stress responses in A. fumigatus. These were further validated by qRT-PCR from RNA extracted under these different conditions. For DCs, we outlined the activation of metabolic pathways in response to the confrontation with A. fumigatus. We found the fatty acid metabolism plays a crucial role, along with other metabolic changes. Transcriptome data and their analysis illuminate additional regulatory pathways activated in the DCs apart from interleukin regulation. We identified subnetworks and several novel key regulators such as UBC, EGFR, and CUL3 of DCs to be activated in response to A. fumigatus.		

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Omer Faruk	Bay	United Kingdom	The University of Manchester
Title:	**Metabolomic and metagenomic analysis of Trichuris muris gut microbiota**		
Author keywords:	Trichuris, Metabolic, Pathway, Metagenomic, Microbiota		
Abstract:	The intestine of mammals is a large habitat not for only bacteria but also for gut dwelling parasites. Cohabitation of microbiota and parasites within the mammalian intestine has contributed the coevolution of these three organisms in a close association for millions of years. The alteration of the intestinal microbiota in rodents by Trichuris muris infection is well established. It has been recently demonstrated that T. muris requires a distinct microbiota from the host intestine for its fitness. In addition, it has been also shown that mice mono colonised with Bacteroides thetaiotaomicron can support an infection by T. muris indicating this single bacterium can supply the necessary requirements for the viability of T. muris. In this PhD project, draft metabolic pathways will be constructed using currently annotated T.muris and B.thetaiotaomicron genome for their comparison to find the close relationship between them. Flux Balance Analysis will be performed in order to find what the worm and the bacterium might provide each other. Then metagenomic studies will be carried out to have an idea about the function of the whole microbiota within the whipworm gut.		

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Title:	**Drug Target Detection in Metabolic Networks as an Optimality Problem**		
Author keywords:	Optimality principles, Drug targets, Metabolism		
Abstract:	Optimality Principles have played a major role in biological systems, from describing mechanisms to being able to predict from first principles to the design of organisms. In this work, we present a dynamic optimization strategy to determine drug targets of pathological dynamic metabolic networks. This methodology involves testing the influence of inhibitors, i.e. the control profiles, via different modes-of-action to the enzymes in the network, and driving the network to a desired healthy state through the maximization or minimization of one or multi-objectives set a priori. The proposed solution of the optimization problem involves using a combination of epsilon - constraint and control vector parametrization (CVP) to obtain non-linear programming problem (NLP) and initial value problem (IVP), which are solved by enhanced scatter search (eSS) optimization metaheuristic implemented in the AMIGO2 toolbox [1]. Using a glycolysis dynamic-model of Trypanosoma brucei, we show a scan for vulnerable enzymes in the model that are probably good drug targets. This project has received funding from the EU Horizon 2020 Research & Innovation Program under the Marie Skłodowska-Curie Grant Agreement #675585. References 1. Balsa-Canto E., et al., (2016), Bioinformatics, 32, 3357.		

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Title:	**Automatic construction and analysis of GECKO-constrained metabolic network models**		
Author keywords:	Flux Balance Analysis, E. coli, Enzymatic constraints, Constraint-based modeling		
Abstract:	Many methods for the analysis of stoichiometric metabolic models are based on Flux Balance Analysis (FBA). In order to improve the accuracy of FBA predictions, several new FBA-derived methods have been developed, which intend to integrate additional biochemical information. One of these methods is GECKO (Genome-scale model with Enzymatic Constraints using Kinetics and Omics data) [1], which allows the incorporation of enzyme kinetics (kcat) and enzyme concentration data in order to further constrain stoichiometric metabolic models. While GECKO has been proven to deliver a useful extension for the consensus genome-scale model of S. cerevisiae [1], there is no easy way to create and analyze a GECKO-extended version of other models. In this work we developed a toolbox allowing an almost fully automated creation of GECKO-enhanced models starting with a standard stoichiometric model as input. In particular, this includes the read-out of the relevant enzymatic data from the SABIO-RK database and the reconfiguration of the stoichiometric model to embed the enzymatic constraints. Additionally, several analysis tools have been developed supporting the fitting of GECKO-relevant constraints and parameters. We applied our new toolbox by generating and analyzing a GECKO-enhanced model of the E. coli genome-scale model iJO1366. We will present major properties of this model and compare it with the standard genome-scale model as well as with other methods that integrated enzymatic data in E. coli models. [1] Mol Syst Biol. (2017) 13: 935		

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Title:	**NAD+ driven transcriptional regulation as a key promoter of yeast metabolic oscillations**		
Author keywords:	Metabolic oscillations, Redox system, Chromatin remodeling		
Abstract:	Sustained oscillations over a large portion of the yeast's transcriptome and metabolome occur in both synchronized populations and single cells. The oscillations have been shown to operate in the absence of the cell division cycle progression and to be robust against changes in temperature. These facts point to the existence of an autonomous metabolic timekeeper. Our current understanding of this phenomenon suggests that temporal regulation is at the level of transcription, most probably relying on epigenetic modifications. Among the metabolites that exhibit pronounced oscillations, NAD+/H is one of the few that also has a high degree of connectivity in the metabolic network, which means it is an important indicator of the cell's metabolic status. Moreover, the metabolite has a direct link to the regulation of gene expression through the NAD+-dependent histone deacetylases. NAD+/H is, thus, an attractive hypothetical central player in the mechanism underlying metabolic oscillations. Indeed, experiments on yeast populations have shown that perturbations of the cell's redox system significantly alters their metabolic periodicity. In this work we explore the role of NAD+/H as the species linking metabolism and transcriptional regulation. We propose and analyze an ordinary differential equation model consisting of the anabolic and catabolic reactions accounting for the main NAD+/H interconversion flux and their transcriptional modulation by chromatin remodeling factors. Our results reproduce the dynamics reported in experimental data for gene expression and metabolite fluctuations.		

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Stefan	Schuster	Germany	Department of Bioinformatics, Matthias Schleiden Institute, University of Jena
Title:	**Kinetic Analysis of the minimal model to describe metabolic oscillations in Bacillus subtilis biofilms**		
Author keywords:	Metabolic Modelling, Oscillations, Hopf Bifurcation, ODE-based model, Michaelis Menten kinetics		
Abstract:	Biofilms are composed of microorganisms attached to a surface or floating on top of a liquid surface. They pose challenges in the field of medicine but can also have useful applications in industry. Regulation of biofilm growth is complex and still largely elusive. Oscillations are thought to be essential for biofilms to cope with nutrient starvation and chemical attacks. Recently, a minimal mathematical model has been employed to describe the oscillations in Bacillus subtilis Biofilm. In this paper, we have investigated four different modifications to the same model in order to better understand the oscillations in Biofilms. Our first modification is towards making a gradient of metabolites from the center of the biofilm to the periphery in which we found that it does not improve the model and is therefore unnecessary. We then use realistic Michaelis Menten kinetics to replace the highly simple mass action kinetics. Further, we use reversible reactions to mimic the diffusion in biofilms. As the final modification, we check the combined effect of using Michaelis Menten kinetics and reversible reactions on the model behavior. We found that the model with Michaelis Menten kinetics along with reversible reactions is the most powerful for the biofilm oscillation system because it shows oscillations when the rate of forward reactions equals the rate of backward reactions and is thus the most accurate description of the biological scenario among all the four variations.		

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Ralf	Steuer	Germany	Humboldt-Universität zu Berlin
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Title:	**Modeling microbial communities using biochemical resource allocation analysis**		
Author keywords:	Cyanobacteria, Photosynthesis, Microbial ecology, Ecosystems biology, Phototrophic growth, Microbial physiology, Growth laws, Protein allocation		
Abstract:	To understand the functioning and dynamics of microbial communities is a fundamental challenge in current biology. To tackle this challenge, the construction of computational models of interacting microbes is an indispensable tool. There is still a large chasm, however, between ecologically-motivated descriptions of microbial growth used in many current ecosystems simulations, and detailed metabolic pathway and genome-based descriptions developed within systems and synthetic biology. Here, we seek to demonstrate how computational resource allocation models of microbial growth, developed in the context of systems biology and metabolic engineering, offer the potential to advance ecosystem simulations and their parameterization. In particular, recent work on quantitative resource allocation allow us to formulate mechanistic models of microbial growth that are physiologically meaningful while remaining computationally tractable. Computational resource allocation models go beyond Michaelis-Menten and Monod-type growth models, and are capable to account for several emergent properties that underlie the remarkable plasticity of microbial growth. We exemplify our approach using a coarse-grained model of cyanobacterial phototrophic growth, and demonstrate how the model allows us to represent the physiological acclimation of cyanobacteria to different environments, co-limitation of growth by several nutrients, as well as emergent metabolic switches between alternative nutrient sources. Our approach has implications for constructing models of microbial communities to understand their interactions, dynamics and response to environmental changes.		

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Costas	Maranas	United States	The Pennsylvania State University
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Title:	**Updated genome-scale metabolic model of Clostridium thermocellum DSM1313 with standard-conforming organization and improved prediction accuracy**		
Author keywords:	Clostridium thermocellum, Consolidated bioprocessing, Network reconstruction, Bioenergy and Biofuels, Metabolic flux analysis		
Abstract:	Our exponentially growing world population requires a sustainable bioeconomy from renewable and carbon neutral production of energy and materials using lignocellulosic biomass and organic wastes. Consolidated bioprocessing (CBP) is a promising technology that utilizes a CBP microorganism capable of performing biomass hydrolysis and fermentation in a single step. Clostridium thermocellum is a gram positive thermophilic CBP bacterium capable of efficient degradation of untreated lignocellulosic biomass, such as poplar or switchgrass, to produce biofuels and biomaterial precursors. However, C. thermocellum has complex and poorly understood metabolism hindering metabolic engineering to achieve high rates, titers, and yields of industrially relevant chemicals, e.g., alcohols and esters. In this study, we developed an updated genome-scale model of C. thermocellum, named iCBI655, to account for recent discoveries in the metabolism of C. thermocellum, improve the predictability of the model by training it with a broad dataset of experimental fluxes and against known lethality phenotypes, and increase its accessibility and reproducibility through extensive documentation and standard-conforming model organization. Furthermore, we illustrated the use of the model to generate biological insights from published datasets by simulating intracellular fluxes consistent with measured metabolite secretion fluxes. We anticipate the new model will be useful for studying physiology, metabolism, and regulation of C. thermocellum and metabolic engineering.		

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Roman	Rainer	Germany	Humboldt-Universität zu Berlin
Christina	Iwert	Germany	Charité University Medicine Berlin
Katja	Tummler	Germany	Humboldt-Universität zu Berlin
Birgit	Sawitzki	Germany	Charité University Medicine Berlin
Edda	Klipp	Germany	Humboldt-Universität zu Berlin
Title:	**Modelling the effect of knock-in Tcaim in Central Carbon Metabolism of T-Cells**		
Author keywords:	T-Cells, Modelling, Central Carbon Metabolism, Tcaim		
Abstract:	Effector T-Cells that overexpress Tcaim (T-cell activation inhibitor, mitochondrial) have morphologically different mitochondria and are less prolific compared to the wild-type effector T-Cells. Microscopic images of T-Cells overexpressing Tcaim show fused mitochondria and dense cristae structure. Such structural issues make it reasonable to assume that the respiratory chain efficiency is affected, leading to slower metabolism. However, the effect on the central carbon metabolism is not understood in detail. To test the hypothesis of the reduced respiratory chain efficiency, intracellular metabolite concentration and uptake rates of supernatant compounds were measured and used to calibrate an ODE (Ordinary Differential Equation) model that explores the differences in the flux distributions and kinetic parameters in the central carbon metabolism between wild-type T cells and T cells that overexpress Tcaim. The differences in metabolism were found by the use of L1-regularization in the parameter estimation. Thereby, we want to understand the effect of Tcaim on metabolic rerouting essential for T-cell activation.		

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Steffen	Klamt	Germany	Max Planck Institute for Dynamics of Complex Technical Systems
Sabine	Koch	Germany	Max Planck Institute for Dynamics of Complex Technical Systems
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Udo	Reichl	Germany	Max Planck Institute for Dynamics of Complex Technical Systems
Title:	**RedCom: A strategy for metabolic modeling of microbial communities and its application for analyzing experimental datasets from anaerobic digestion**		
Author keywords:	Microbial Communities, Metabolic modeling, Elementary flux vectors, Anaerobic digestion, Biogas plants		
Abstract:	Microbial communities are involved in many fundamental processes in nature, health and biotechnology. Constraint-based modeling is increasingly used to analyze these communities, however, compared to single-species models, stoichiometric community models are markedly more complicated due to (i) their increased size, (ii) their bilinear nature, and (iii) many biologically unrealistic behaviors in their solution space. Here we present RedCom, a new approach to build reduced stoichiometric models of balanced microbial communities based on net conversions of the single-species models [1]. We show that the concept of elementary flux vectors (EFVs) is well-suited to identify those net conversions and that discarding EFVs violating a minimality criterion in the exchange fluxes removes regions in the solution space with unrealistic altruistic behavior of certain species. We demonstrate the applicability of our RedCom approach by modeling communities of up to nine organisms involved in degradation steps of anaerobic digestion. We show that, compared to full community models, RedCom models have not only a greatly reduced size but also a higher predictive power because their feasible ranges of community compositions and exchange fluxes are much smaller but still consistent with measurements obtained from enrichment cultures. As one of the first studies in this field, we also used metaproteomic data from an enrichment culture (growing on ethanol) to further constrain the solution space of the model for this community. Both model and proteomic data indicate a dominance of acetoclastic methanogens (Methanosarcinales) and a low abundance of Desulfovibrionales. [1] Koch et al. (2019), PLOS Comp Biol, 15:e10006759.		

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Soukaina	Timouma	United Kingdom	The University of Manchester
Title:	**Mining and modeling the genome of yeast industrial hybrids**		
Author keywords:	Yeast, Genome-scale model, FBA, Optimization		
Abstract:	The budding yeast Saccharomyces cerevisiae, with its related species and hybrids are the organisms of choice used in wine and beer industry. In this PhD project, we are interested in Saccharomyces pastorianus, a natural hybrid with unique industrial properties, such as ability to ferment at low temperatures and under stressful conditions. The strains belonging to S. pastorianus evolve from hybridisation events between the mesophilic S. cerevisiae and the cold tolerant S. eubayanus. Modelling metabolic pathways has been successfully applied to S. cerevisiae in order to inform genome manipulation to optimise the production of desired compounds. The availability of a complete genome sequence for S. pastorianus hybrids makes it possible to reconstruct a full genome-scale metabolic model (GEM) for this species. Once the model is available, Flux Balance Analysis (FBA) can be used to predict growth in different environments. The OptKnock algorithm can predict combinations of gene deletions that optimise for the production of specific compounds and metabolites, such as isoamyl-acetate, an important flavour compound. New methods enable the integration of absolute transcriptome data into Flux Balance Analysis (FBA) for improved quantitative flux predictions.		

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Szabolcs Cselgő	Kovács	Hungary	Biological Research Centre of Szeged
Balázs	Szappanos	Hungary	Biological Research Centre of Szeged
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Title:	**Potential of underground metabolism for the bioproduction of value-added compounds**		
Author keywords:	Underground activity, Metabolic engineering, Value-added compound, In silico		
Abstract:	Bioproduction of industrially relevant compounds is frequently attained by utilising enzymes from other species, that is, heterologous enzymes. However, overexpression of heterologous enzymes is often detrimental due to unexpected interactions with the host cell. Recently, an alternative strategy has been proposed which utilises the side activities of the host enzymes to build new biosynthetic pathways. Such low-level 'underground' enzyme activities are prevalent and can be enhanced by enzyme engineering, making them an ideal surrogate to heterologous metabolic steps. However, apart from a handful of case studies, no systematic work has been devoted to explore the potential of underground reactions in engineering biosynthetic pathways. To fill this gap in our knowledge, we extended the genome-scale metabolic reconstruction of Escherichia coli with 558 underground reactions and explored its potential to produce valuable compounds in silico. Out of 207 compounds tested, underground reactions enhanced the yield of 28 compounds and allowed the production of 5 additional compounds which were not producible by the native E. coli network. Furthermore, we found that the capacity of underground reactions to produce industrially relevant compounds is similar to that of heterologous reactions. We conclude that utilising underground enzyme activities is a promising addition to the toolbox of industrial strain development.		

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Suraj	Sharma	Norway	UiT The Arctic University of Norway
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Title:	**NAD – A dynamic hub for metabolism and signaling**		
Author keywords:	NAD Metabolism, Cofactor Dynamics, Metabolic Modelling, Systems Medicine		
Abstract:	Nicotinamide adenine dinucleotide (NAD) dependent signalling is essential for cellular gene regulation and signalling, participating e.g. in DNA damage repair, histone-modifications and Ca-signalling. These processes consume considerable amounts of NAD, causing the turnover of cellular NAD pools in only a few hours. If this is not matched by an equally rapid NAD biosynthesis NAD concentrations decline, effecting a large number of metabolic reactions. Reduced NAD concentrations, most likely caused by imbalances between NAD biosynthesis and consumption have been observed in a number of mainly age-related diseases, including neurodegeneration, obesity and cancer. To develop treatments targeting these diseases, it is important to understand the dynamics of NAD metabolism and its impact on NAD dependent or interconnected pathways. We, therefore, built a mathematical model of NAD biosynthesis and consumption and linked it to representative redox reactions. This enables us to simulate the effect of alterations in NAD biosynthesis and consumption on different cellular pathways, such as fatty acid metabolism or the metabolism of other co-factors such as S-adenosyl-methionine (SAM). Our analyses reveal a complex interplay between the metabolism of different co-factors that likely play an important role in the development of different diseases.		

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Title:	**Applying genome-scale metabolic modelling to study biofilm-formation in S. epidermidis involved in prosthetic joint infections**
Author keywords:	Genome-scale metabolic modeling, Staphilococci, Biofilms, Prosthetic joint infections
Abstract:	Prosthetic joint infections occur when bacteria manage to colonise an implant by forming a biofilm. Once stablished, biofilms are difficult to eliminate, making treatments expensive and aggressive and constituting a major burden to the health care system and the patients. Non-aureus staphylococci account for approximately 30% of the cases, with S. epidermidis being the species most commonly isolated. Understanding how it grows and produces biofilms will inform the diagnosis and management of this condition. Using the software package ScrumPy, a genome-scale metabolic model of S. epidermidis has been constructed and subsequently curated and validated applying linear programming techniques. It consists of 976 reactions and 862 metabolites, with all reactions atomically balanced in terms of C, N, P, S, O and H. The model is free of energy inconsistencies and capable of generating all biomass components from a minimal medium in the proportions experimentally described. In addition, experimental data on minimal growth requirements and utilisation of amino acids has been used for further validation. The system is capable of reproducing metabolic strategies observed in vitro, such as the incomplete oxidation of glucose to pyruvate and the subsequent production of acetate under aerobic conditions, in what seems to be an optimal response for ATP production and minimisation of protein investment. Current analysis are focused on identifying metabolic strategies that allow growth in the joints and production of biofilm biomass and the results obtained are presented here.

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Xiao-Pan	Hu	Germany	Heinrich Heine University Düsseldorf
Hugo	Dourado	Germany	Heinrich Heine University Düsseldorf
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Title:	**The concentrations of the gene expression machinery in Escherichia coli are optimized for maximal efficiency**		
Author keywords:	Transcription, Translation, Mathematical model, Physicochemical constraints, RNA polymerase, Ribosome, Ribosome activity, Growth laws, Growth-rate-dependent macromolecular composition		
Abstract:	The most central and most expensive process of biological cells is gene expression, comprising transcription and translation. Experimentalists have investigated the economy of gene expression at the cellular level by measuring RNA polymerase partitioning, ribosome activity, and the expression of the participating molecule species. The observed growth-rate dependences form the basis of powerful phenomenological bacterial growth laws; however, a quantitative theory allowing us to understand these phenomena on the basis of fundamental biophysical and biochemical principles is currently lacking. Here, we show that the observed growth-rate dependences of the concentrations of the RNA polymerase, ribosomes, tRNAs, mRNA, and translation elongation factors in Escherichia coli can be predicted accurately by minimizing cellular costs in a detailed mathematical gene expression model; the mechanistic model is only constrained by the physicochemical properties of the molecules and requires no parameter fitting. We approximate the costs of molecule species by their masses, justified by the observation that cellular dry mass per volume is roughly constant across growth rates and hence represents a limited resource. Our results also account quantitatively for observed RNA polymerase partitioning, RNA/protein ratio, ribosome activity, and cellular RNA composition of E. coli across diverse growth conditions, including antibiotic stress. We conclude that the growth-rate-dependent composition of E. coli's gene expression machinery is a consequence of natural selection for minimal total cost under physicochemical constraints, a paradigm that might be applied to understand the organization of other complex biological systems.		

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Tim	Nies	Germany	Institute for Quantitative and Theoretical Biology, Heinrich-Heine-Universität Düsseldorf
Oliver	Ebenhöh	Germany	Institute for Quantitative and Theoretical Biology, Heinrich-Heine-Universität Düsseldorf
Title:	**Characterization of Flux Cones for Inferring Microbial Metabolism in Dynamic Simulations**		
Author keywords:	Microbial communities, Stoichiometric network analysis, Niche occupation, Organismic interactions, Elementary modes, Extreme pathways, Dynamic simulations		
Abstract:	The simulation of microbial dynamics is an area of active research that was and still is investigated using a plethora of theoretical and experimental methods. Over the last few years the rise of constraint based modeling in form of Flux Balance Analysis and its combination with dynamic information (dFBA) resulted in many insights of the assembly and dynamics of microbial populations. However, classical ordinary differential equation based models are still actively used and possess the potential to explain fundamental organizational principles in the formation of microbial ecosystems. Based on an extended MacArthur consumer resource model of community dynamics proposed by Marsland III et al. (Plos Comp. Bio., 2019) accounting for byproduct synthesis of a species by a simple matrix D, we show how this matrix can be inferred using computational geometry and novel algorithms of stoichiometric network analysis. Utilizing diverse approaches such as elementary mode and extreme pathway analysis we characterize the underlying flux cones of genome scale models and integrate this information in the dynamical description of microbial ecosystems. Finally, with this combination of convex analysis and population dynamics of different microbial species we illustrate the effect of evolutionary strategies on the dynamics of how environmental niches are occupied in complex communities. By exploring the combinatorial space of the initial composition in our in silico microbial assemblies and thus covering a big part of the organismic interaction spectrum we show that microbial populations are a highly organized biological structure that follows its own laws and rules.		

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Edwin	Chingaté	Colombia	Universidad Nacional de Colombia
Andrés	Pinzón	Colombia	Universidad Nacional de Colombia
Title:	**Simulation of an anodic chamber and effect of its composition over microbial fuel cell performance.**		
Author keywords:	Microbial Fuel Cell, Metabolic model, Geobacter Sulfurreducens, Biofilm		
Abstract:	Microbial fuel cells (MFC) technology is a promising sustainable technology for energy generation. Although there has been a growing research on this topic, there is no comercial prototype available yet. Therefore, it is necessary to deepen our understanding on the microbial communities in order to develop microbial fuel cell devices with better performance. In this work, a MFC was simulated varying substrates and microbial diversity, analogous to a sewage treatment cell. Genome scale metabolic models for typical microorganisms, such as Geobacter Sulfurreducens, in MFC environment were revised and refined with this purpose. These models were integrated using the R package "BacArena" and the microorganisms were allowed to interact dynamically by partial oxidized metabolites exchange. The "BacArena" environment was allowed to develop a biofilm as an emerging property. The concentration of some added substrates was varied too. Our simulations showed that there are some substrates that stimulate the domain of microorganisms that do not have significant participation in electric work generation, and other substrates with the opposite effect. As final remark, hereby we present the first computational model of a MFC based on the interaction of metabolic models from different microorganisms.		

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Yvan	Rousset	Germany	Institut für Quantitative und Theoretische Biologie
Title:	**Mathematical modelling of glycogen metabolism and glycogen-related disorders.**		
Author keywords:	Glycogen, Mathematical modeling, Rare metabolic disease, Stochastic simulation		
Abstract:	Metabolic diseases, that affect both energy storage and consumption, are a burden on the European population and health care system. In the PoLiMeR project we focus on rare metabolic diseases and the regulation of polymers in the liver: fatty acids and glycogen. Glycogen, a multi-branched polymer made of glucose chains, serves as energy storage in animals, fungi and bacteria. In humans, glycogen is mostly found in the liver and muscles. When energy is needed, the glycogen stored in the liver can be broken down into glucose units and circulate through the blood to fuel other organs. From a structural point of view, glycogen is made of linear chains of glucose residues and branching points. The regularity of chains length and branching pattern leads to a spherical, highly ordered, branched polymer. Under normal conditions the glycogen structure maximizes two fundamental properties: overall glucose storage and availability of the substrate for degradation. Despite a relatively small number of enzymes involved in glycogen biogenesis and degradation, the detailed mechanistic and kinetic aspects, are still unclear. I will present a toy model of glycogen formation using stochastic simulations that requires a small number of parameter such as the enzyme concentrations involved in the process. I will show how these parameters may impact the glycogen structure, and whether it is optimal. The model will contribute to reproduce metabolic disorders related to glycogen metabolism and support the development of intervention strategies to counteract glycogen-related metabolic disorders by drug applications.		

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Takeyuki	Tamura	Japan	Kyoto University
Title:	**Growth-coupled overproduction is theoretically possible for most metabolites in Saccharomyces cerevisiae under anaerobic condition**		
Author keywords:	growth coupling, flux balance analysis, algorithm, deletion strategy		
Abstract:	Metabolic network analysis through flux balance is an established method for the computational design of production strains in metabolic engineering. A key principle often used in this method is the production of target metabolites as by-products of cell growth. Recently, the strong coupling-based method was used to demonstrate that the coupling of growth and production is possible for nearly all metabolites through reaction deletions in genome-scale metabolic models of Escherichia coli and Saccharomyces cerevisiae under aerobic conditions. However, it is unknown whether this coupling, using reaction deletions, is always possible under anaerobic conditions. In fact, when growing S. cerevisiae under anaerobic conditions, deletion strategies using the strong coupling-based method were possible for only 3.9% of all metabolites. Here, we found that the coupling of growth and production is theoretically possible for 91.3% metabolites in genome-scale models of S. cerevisiae under anaerobic conditions if any reaction deletion strategy is allowed. This analysis was conducted for the worst-case-scenario using flux variability analysis. To demonstrate the feasibility of the coupling, we derived appropriate reaction deletions using a new algorithm for target production in which the search space was divided into small cubes (CubeProd). Our results are fundamentally important for computational metabolic engineering under anaerobic conditions. The developed software, CubeProd, implemented in MATLAB, and the obtained reaction deletion strategies are available at (http://sunflower.kuicr.kyoto-u.ac.jp/~tamura/CubeProd.zip).		