International Federation of Automatic Control
in Cooperation with the CACHE Corporation

## Program Booklet

# FOSBE 2016

# 6th International Conference on Foundations of Systems Biology in Engineering

**Magdeburg, Germany, October 9-12, 2016**

Edited by
Rolf Findeisen, Otto von Guericke University Magdeburg, Germany
Eric Bullinger, Otto von Guericke University Magdeburg, Germany
Eva Balsa-Canto, IIM-CSIC, Spain
Kristel Bernaerts, KU Leuven, Belgium
**Maps/Points of Interest FOSBE 2016**

FOSBE 2016, Magdeburg

# Program at a Glance

### Sunday October 9

| | |
|---|---|
| 13:30-17:00 SuW1, G28 room 026 **Workshop: Optimization in Systems and Synthetic Biology: Concepts, Methods and Illustrative Examples** | 13:30-17:00 SuW2, G28 room 027 **Workshop: Kinetic and Optimization Based Models for Understanding the Regulation of Cellular Metabolism** |
| 18:00-20:00 SuRP, G28, **Welcome Reception** | |

### Monday October 10

| | |
|---|---|
| 08:30-08:45 MoOP.    Nave, **Opening** | |
| 08:45-09:30 MoPMP, Nave, **Plenary Guy-Bart Stan** | |
| 09:30-10:00 MoKMP, Nave, **Keynote Robert S. Parker** | |
| 10:00-10:30 MoCMP, Nave, **Coffee Break** | |
| 10:30-12:10 MoM1,    Nave, **Synthetic Biology** | 10:30-12:10 MoM2, Gallery **Modelling – Health** |
| 12:10-14:10 MoPP,    Nave, **Poster Session I with Lunch** | |
| 14:10-15:00 MoPAP, Nave, **Public Plenary Frank Doyle** | |
| 15:10-15:40 MoKAP, Nave, **Keynote Rudi Gunawan** | |
| 15:40-16:10 MoCAP, Nave, **Coffee Break MA** | |
| 16:10-17:50 MoA1,    Nave **Modelling–Microbial Systems** | 16:10-17:50 MoA2, Gallery **Methods** |
| 17:50-19:30 MoCP, **Guided city walk and visit of the Magdeburg Cathedral** | |

### Tuesday October 11

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|---|---|
| 08:30-09:15 TuPMP, Nave, **Plenary Hans Westerhoff** | |
| 09:15-09:45 TuKMP, Nave, **Keynote Bas Teusink** | |
| 09:45-10:20 TuCMP, Nave, **Coffee Break TM** | |
| 10:20-12:00 TuM1, Nave **Dynamics and Control** | 10:20-12:00 TuM2, Gallery **Optimization Based Methods for Understanding the Regulation of Cellular Metabolism** |
| 12:00-14:00 TuPP,     TM, **Poster Session II with Lunch** | |
| 14:00-14:30 TuKA1P, Nave, **Keynote Pablo Iglesias** | |
| 14:30-15:00 TuKA2P, Nave, **Keynote Jörg Stelling** | |
| 15:00-15:20 TuCAP,   Nave, **Coffee Break** | |
| 15:20-17:00 TuA1, Nave **Session in Memoriam of Peter Wellstead** | 15:20-17:00 TuA2, Gallery **Biotechnology Methods & Applications** |
| 17:30-23:00 TuRP, **Conference Banquet and Boat Tour** | |

### Wednesday October 12

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| 08:30-09:15 WePMP, Nave, **Plenary Diego di Bernardo** |
| 09:15-09:45 WeKMP, Nave, **Keynote Birgit Schöberl** |
| 09:45-10:20 WeCMP, Nave, **Coffee Break** |
| 10:20-11:40 WeM1,    Nave, **Systems Medicine** |
| 11:40-12:10 WeKAP, Nave, **Keynote Edda Klipp** |
| 12:10-12:30 WeClP,   Nave, **Closing** |

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# Welcome Message



It is our pleasure to welcome you to the 2016 IFAC Conference on Foundations of Systems Biology in Engineering (FOSBE) in Magdeburg, Germany on behalf of the National Organizing Committee and International Program Committee. The International Federation of Automatic Control (IFAC) and the CACHE Corporation jointly organize FOSBE on a rotating basis. FOSBE aims at stimulating discussion and fostering collaborations among scientists from method and theory oriented engineers to experimental and theoretical biologists.

The program accommodates contributions from various areas and methodologies spanning from multi-scale and multi-omics data integration and modeling to systems medicine.

FOSBE 2016 features a varied scientific program, including plenary lectures, invited keynote presentations, contributed and invited technical sessions, two pre-conference workshops, and a social program that will take you to the cultural heritage sites of the city of Magdeburg. The technical sessions are hosted in the Johanniskirche, a historical church mentioned more than 1160 years ago in 936.

Based on a strict reviewing process, the International Program Committee selected 122 contributions for presentation, 58 regular and brief papers, 56 abstract contributions, as well as four invited plenary and four invited keynote presentations. Three additional keynote presentations have been selected from the submitted contributions. The program consists of eight regular sessions, one invited session, two poster sessions, seven keynote lectures, and four plenary sessions. Each morning begins with a plenary talk followed by a keynote talk. Monday afternoon features an additional plenary talk, which will be open to the public and all members of the university. The program is complemented by two interesting pre-conference workshops that take place on Sunday, October 9.

The social program consists of the opening reception on Sunday evening in the systems biology building of the university, a guided walking tour of the historic Magdeburg, with a visit to the Cathedral, and the Conference Banquet on Tuesday evening preceded by a boat tour on the Elbe river.

The conference would have not been possible without tremendous contributions of the NOC and IPC members, the support and help of all students and assistants, the IPC area chairs who organized review of the papers, and all the reviewers. We would also like to acknowledge the support from conference sponsors.

All participants are invited to explore the long history of Magdeburg and Saxony-Anhalt, which is often referred to as the birth cradle of German history and culture.
Please do not hesitate to stop by at the conference registration desk or contact any volunteer if you have questions or need help. We hope that you will enjoy your stay in Magdeburg.

Best regards,


Rolf Findeisen (NOC chair), on behalf of the NOC

Eva Balsa-Canto (IPC chair), on behalf of the IPC

FOSBE 2016, Magdeburg

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## IPC Area Chairs

| | | |
|---|---|---|
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## IPC Members

| | | |
|---|---|---|
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| Julio Banga (SP) | Pablo Iglesias (US) | Chris Rao (US)Birgit |
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| Olivier Bernard (FR) | Mats Jirstrand (SE) | Guy-Bart Stan (UK) |
| Hidde de Jong (FR) | Rudibert King (DE) | Jörg Stelling (CH) |
| Diego di Bernardo (IT) | Hiroaki Kitano (JP | Bas Teusink (NL) |
| Richard Braatz (US) | Maria Klappa (GR) | Fabian Theis (DE) |
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| Christina Chan (US) | Heinz Koeppel (DE) | Arjan van der Schaft (NL) |
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Center for Dynamical Systems - Biosystems Engineering

Otto von Guericke University Magdeburg

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Processes, MDPI - Open Access Publishing

# Registration, Social Program, Pre-Conference Workshops, Announcements

### Registration Sunday October 9-Wednesday October 12
Sunday 9, 12:30-18:30:
The registration desk can be found on the ground floor of building 28 of the University, Pfälzerplatz, where the conference workshops and the welcome reception will take place, see map at the end of the brochure.

Monday, Tuesday 8:00-18:00; Wednesday October 12, 8:00-12:00:
The registration desk will be located in the entrance area of the Johanniskirche, see map at the end of the brochure.

### Welcome Reception, Sunday October 9, 18:00-20:00
The welcome reception will take place at the building 28 of the University, see map at the end of the brochure. Complimentary drinks and food are provided.

### Guided Magdeburg walking tour, visit of the Cathedral, Monday, 17:50-19:30
The guided Magdeburg walking tour will leave directly after the last session in front of the Johanniskirche.

### Conference banquet and boat tour, Tuesday, 17:30-23:00
The conference banquet will take place in the Park Hotel Herrenkrug (see map at the end of the brochure). It will be preceeded by a boat trip on the river Elbe. The trip will leave from the entrance of the Johanniskirche at 17:30. After the banquet busses will return to the Johanniskirche and Domplatz.

**Please report any dietary requirements as soon as possible to the conference secretary!**

### Pre-Conference Workshops
Two workshops are organized as pre-conference, they do required pre-registration:

- Optimization in systems and synthetic biology: Concepts, methods and illustrative examples,
- Kinetic and Optimization Based Models for Understanding the Regulation of Cellular Metabolism.

The workshops take place in parallel sessions on the afternoon of 9th October, 13:30 – 17:00, building 28, room 26 and 27, Pfälzerplatz, see map at the end of the brochure.

### Wireless Network
Free wireless network will be provided. Please ask at the registration desk for the access code.

# Instruction for Presenters, Session Chairs, Posters

## 1. Oral Presentations
The allocated time for the talks are as follows:

| Type | Presentation time | Discussion time |
| --- | --- | --- |
| Plenary | 40 minutes | 5 minutes |
| Keynote | 25 minutes | 5 minutes |
| Regular | 17 minutes | 3 minutes |

Presentations should be done using MS-Office PowerPoint or Adobe Acrobat. A notebook, a projector, and a pointer with remote control will be available in all session rooms. All presenters should save their presentations on a USB drive in a format readable on a Windows-based PC. Presenters should transfer their files to the notebook at the venue of their presentation before the session, and check the correct appearance of the presentation. An own laptop can be connected with the consent of the session chair. Preferable times are during coffee, lunch and inter-session breaks. A student volunteer will be available to assist the presenters. Presenters are requested to get in contact with the session chair 10 minutes before the beginning of the session.

## *2. Poster Presenters*
The poster sessions take place in the back area of the main hall in the Johanniskirche, close to the main entrance (see map on the last page of the program). The maximum poster size is A0, 841 mm x 1189 mm, portrait orientation. Posters should be put up in the morning before the allocated poster session starts on the presentation day and removed after the session ends. Board pins and tape will be available on-site. There will be a list with the allocated poster slot. Authors should be present during the poster session to explain their work and to interact with fellow attendees. You might consider bringing paper copies of your poster and paper.

## *3. Session Chairs*
Please take note of the day/time/venue of the session that you are chairing in the program booklet. On the day of the session that you are chairing, obtain any changes to the program from the support staff at the Registration Desk.

Before the start of the session, collect the biographical information of the presenting authors. Use this information to briefly introduce the speaker before his/her presentation. Be present in the room where the session is to be held 10 minutes before the start of the session and check that possibly all the presentations have been copied on the notebook provided at the venue. Remind the presenting author about the time available for their presentation; see "Instructions to Authors" for details. Remind the authors at the 2-minute mark (*e.g.*, at the 15th minute of presentation for regular presentations) to make their concluding remarks. Please ensure that there is sufficient time for discussion.

In case of "no-show" or if a talk ends early, do not advance the presentations. The additional time can be used for discussions related to papers presented earlier in the session.

# Plenary Talks

### Systems approaches to treating diabetes

**Francis J. Doyle III**
**School of Engineering and Applied Sciences,**
**Harvard University**

**Abstract:** Diabetes is a disease that afflicts over 400 million individuals worldwide and is characterized by a dysregulation of blood sugar levels in the blood. In type 1 diabetes, the beta cells in the pancreas are destroyed, removing endogenous insulin production and thus necessitating exogenous insulin administration. In type 2 diabetes, the more prevalent version, insulin is produced, but the body fails to respond appropriately. Over the years our group has studied both type 1 and type 2 diabetes, with model-based control systems approaches for the optimal delivery of insulin, and robust control approaches to the identification of drug targets in the cellular regulatory network. I will provide an overview of the systems biology approaches employed by our group to study diabetes, from signaling models to pharmacokinetic/pharmacodynamic patient models. These methods enable the personalized and predictive medicine approaches that are receiving increasing attention. The role of models and control theoretic sensitivity analyses in both drug targeting and drug delivery will be detailed. A novel application of the structured singular value to the glucose signaling network will be shown, with relevance to type 2 diabetes drug targets. Finally, encouraging clinical results from over 1000 individual patient tests will be described, including systems issues for FDA review as well as a path to eventual commercialization.

**Bio:** Frank Doyle is the John A. Paulson Dean of the School of Engineering and Applied Sciences at Harvard University, where he also is the John A. & Elizabeth S. Armstrong Professor. Prior to that he was the Mellichamp Professor at UC Santa Barbara, where he was the Chair of the Department of Chemical Engineering, the Director of the UCSB/MIT/Caltech Institute for Collaborative Biotechnologies, and the Associate Dean for Research in the College of Engineering. He received a B.S.E. degree from Princeton, C.P.G.S. from Cambridge, and Ph.D. from Caltech, all in Chemical Engineering. He has also held faculty appointments at Purdue University and the University of Delaware, and held visiting positions at DuPont, Weyerhaeuser, and Stuttgart University. He has been recognized as a Fellow of multiple professional organizations including: IEEE, IFAC, AIMBE, and the AAAS. He is the President for the IEEE Control Systems Society, and is the Vice President of the International Federation of Automatic Control. In 2005, he was awarded the Computing in Chemical Engineering Award from the AIChE for his innovative work in systems biology, and in 2015 received the Control Engineering Practice Award from the American Automatic Control Council for his development of the artificial pancreas.

**Controlling gene expression from inducible promoters in yeast and mammalian cells**

**Diego di Bernardo**

**University of Naples "Federico II"**

**Abstract:** A crucial feature of biological systems is their ability to maintain homeostasis in spite of ever-changing conditions. In this talk, I will show how the engineering feedback control paradigm can be applied in synthetic biology in order to force a the expression of a gene to be in a desired range, or to change in time with a desired dynamics (e.g. pulsatile expression, sinusoidal expression etc.) from inducible promoters.  Examples on the control of gene expression in yeast and mammalian cells will be shown.

**Bio:** Diego di Bernardo received the "Laurea cum laude" in Electronic Engineering in January 1997 by the University of Naples "Federico II". In 2001, thanks to a single three-year scholarship "Marie Curie" of the European Commission, received Ph.D. (PhD) from the University of Newcastle School of Medicine, UK, in the laboratory of Prof. Alan Murray. Until April 2002 he was postdoctoral researcher at the Wellcome Trust Sanger Center in Cambridge (United Kingdom) in the laboratory of Dr. Tim Hubbard. From May 2002 to December 2002 was postdoctoral researcher in the laboratory of Prof. Jim Collins in the Department of Bioengineering at the University of Boston, USA. Since January 2003 he is an independent researcher (Principal Investigator) at the Telethon Institute of Genetics and Medicine in Naples (TIGEM) where he directs the Genetics, Genomics and Systems Biology research program. In November 2007 he became Assistant Professor at the University of Naples "Federico II" and in November 2015 Associate Professor in Biomedical Engineering at the Dept. of Chemical, Materials and Industrial Engineering.  He is currently Associate Editor of the IEEE / ACM Trans Comput. Biol. and Bioinform. He coordinated national European and international research projects in the field of Systems and Synthetic Biology (including European Union FP6, FP7 and H2020, HFSP, Italian Telethon Foundation and the Italian Ministry of Health).

**Control engineering meets synthetic biology: shared resources and feedback considerations for better engineering of bacterial cells**



**Guy-Bart Stan**
**Imperial College London**

**Abstract:** In this talk I will give an overview of some of our research activities in the "Control Engineering Synthetic Biology" group, where we focus our efforts on developing foundational forward-engineering methods to mathematically model, control, and experimentally implement synthetic gene circuits and cellular systems that aim at increasing the robustness, performance, and genetic stability of engineered cells. During the talk, I will propose some approaches to answer the following core questions in systems and synthetic biology:
*   How can we design taking into account shared resources to improve growth rates, genetic stability and robustness of synthetic biology systems?
*   How can we improve the dynamic performance (e.g. transient and response time) of synthetic biology systems?
*   How can we use cellular resources more efficiently to simultaneously improve growth rates and production yields?

In particular, I will present some recent work on the development of various de novo biomolecular feedback mechanisms in bacterial cells (mainly *E. coli*) that we use to answer the above questions. Our envisioned target applications for these novel designs include cell-based medicine, more efficient biosynthesis, and scale-up in synthetic biology and biotechnology.

**Bio:** Dr. Guy-Bart Stan is a Reader (equiv. Associate Professor) in Engineering Design for Synthetic Biology and the head of the "Control Engineering Synthetic Biology" group at the Department of Bioengineering of Imperial College London, U.K. Dr. Stan received his PhD in Applied Sciences (mathematical analysis and control of nonlinear dynamical systems) from the University of Liege (Belgium) in March 2005 and subsequently worked for Philips Applied Technologies as Senior Digital Signal Processing Engineer and Coordinator of the R&D teams at Eindhoven (The Netherlands) and Leuven (Belgium). From January 2006 until December 2009, he was as Post-Doctoral Research Associate in the Control Group of the Department of Engineering at the University of Cambridge, first supported by a EU Marie Curie Intra-European Fellowship (Jan 2006-Dec 2006) and then by the UK EPSRC (Jan 2007 - Dec 2009). He joined the Department of Bioengineering at Imperial College London in December 2009 as a founding member of the Centre for Synthetic Biology and Innovation (http://www.imperial.ac.uk/synthetic-biology). He is one of the recipients of the prestigious UK EPSRC Fellowship for Growth in Synthetic Biology.

**Maps for when the living gets tough: Maneuvering through a hostile energy landscape**

**Hans V. Westerhoff**

**University of Amsterdam**
**VU University Amsterdam**
**University of Manchester**

**Abstract:** With genome sequencing of thousands of organisms, a scaffold has become available for data integration: molecular information can now be organized by attaching it to the genes and their gene-expression products. But of course, it is the genome that is selfish not the gene. By using mass conservation and balance relationships, the metabolic part of the functioning genome can be organized into a maps that enable functional interpretation of the fitness of the genome, and hence of its genes collectively. Using flux balance analysis one can liven up such genome-wide metabolic maps and calculate the theoretical capabilities of the living organism. Here we shall discuss how this elucidates how organisms such as the ones present when life on earth began, are able to assimilate the Gibbs energy and Carbon that Life needs for its reproduction and maintenance, from their Gibbs-energy-poor environment. We shall address how *C. ljungdahlii* may use at least two special features and one special pathway to this end, i.e. gear-shifting, electron bifurcation and the Wood-Ljungdahl pathway. The gear-shifting is needed because of the fairly high Gibbs energy quant in ATP. We will discuss a similar network-based gear shifting in *S. solfataricus*. Since the Wood-Ljungdahl pathway uses hydrogen gas and has CO as an intermediate, we examined whether the *C. ljungdahlii* map can also help solve a less academic problem, i.e. the management of waste. We find that the organism itself might be able to turn hydrogen gas and CO, which as syngas becomes available upon incineration of waste, into biodegradable plastic, provided it is engineered with two additional genes.

**Bio:** Hans Westerhoff is a long time researcher of how dynamic interactions between components of biological systems generate function. He started this in bioenergetics, non-equilibrium thermodynamics, and metabolic control analysis. After a PhD at the University of Amsterdam and stays at the University of Padova, the US National Institute of Health and the Netherlands Cancer Institute, he is now Professor of Synthetic Systems Biology at the University of Amsterdam, Professor of Systems Biology and Director of the Manchester Doctoral Training Centre for Systems Biology at the University of Manchester, and Professor of Microbial Physiology at the VU University Amsterdam. He is one of the drivers of the silicon human initiative and the Infrastructure for Systems Biology Europe (ISBE). He has been involved in determining molecular biochemistry properties of bacteriorhodopsin, DNA gyrase and various glycolytic enzymes of yeast and *E. coli*, as well as control and regulation aspects in microbial and mammalian cells.

# Invited Keynote talks

## Yeast Mating in Space and Time

**Edda Klipp**
**Humboldt-Universität zu Berlin, Germany**

**Abstract:** Baker's yeast (*Saccharomyces cerevisiae*) has a diploid lifestyle, but under stress conditions it forms spores which then release haploid cells of mating types MATa and MATα. MATa cells are a frequently used model organism for many cell biological studies of cell cycle, metabolism or signaling. MATa and MATα cells can also mate to form diploid cells again. To this end they secrete the pheromones a-factor and α-factor, sense the opposite pheromone and form protrusions in the direction of a potential mating partner. Importantly, they cannot move towards their mating partner, thus the formation of the mating shape called shmoo is a significant investment. Combining experimental studies of the cellular responses to mating factor and the resulting shape changes with spatial mathematical modeling, we investigated three major steps in the mating process. Specifically, we asked (i) how yeast cells communicate to form sharp gradients allowing precise decisions, (ii) how the individual cells sense the resulting gradients and (iii) how they translate the sensed information into shape changes.

**Bio:** Edda Klipp is full professor for Theoretical Biophysics at Humboldt-Universität zu Berlin since 2008. She has a doctoral degree in theoretical biophysics and held a position as research scientist at Humboldt-Universität following a postdoctoral period in Berlin. From 2001 to 2006, she was junior research group leader in "Kinetic modeling" before taking over the head of the research group "Computational Systems Biology" at Max-Planck Institute for Molecular Genetics until 2008. In 2009 she was awarded an honorary doctor of Göteborg University. 2015 she was awarded the Caroline-von-Humboldt professorship at Humboldt-Universität zu Berlin. Prof. Klipp is a founding member of the International Society of Systems Biology, member of several scientific advisory boards for systems biology consortia and institutions and she is principal investigator in several European and national research consortia for systems biology. She organizes a graduate program in Computational Systems Biology in Berlin.

**Regulation of metabolism: navigating between desired and fatal states**

**Bas Teusink**
**Vrije Universiteit Amsterdam**

**Abstract:** Cells evolved a remarkable ability to adapt to environmental conditions, or to withstand otherwise detrimental mutations. These properties arise from the integrative functioning of biological networks. Functional genomics has allowed the cost-effective measurement of the network components; however, we still mostly fail to understand how their interactions lead to cellular function and adaptation. One view that is becoming dominant in cellular physiology, is that physical and (bio)chemical constraints limits protein content and synthesis, impacting how resources are partitioned over growth and stress processes to optimize fitness ("cellular economics"). This view contrasts current mainstream modeling efforts at the genome-scale, which are largely focussed on the metabolic network only, and subsequently they often fail to predict the proper regulation of fluxes. I will show with some practical examples, however, when and how these models are still useful, and how we can integrate the cellular economy into these models. Still, the resource allocation perspective is developed for steady-state growth under constant environments, and mostly for *E. coli*. Whether this perspective is relevant for other microorganisms remains unclear. Moreover, what happens during transitions between steady-state growth conditions is largely unexplored. Recent studies in yeast show that the response time after a nutrient change is an evolvable trait that is dependent on nutrient dynamics and comes at the cost of balanced growth rate. We showed that an intricate and dynamic regulatory mechanism is in place in yeast to ensure robustness during glucose transitions. Thus, the aim of this talk is to illustrate how regulation of metabolism is an intruiging balancing act between desired and fatal states, shaped by constraints and trade-offs.

**Bio:** Prof. Dr. Bas Teusink studied (Bio)Chemistry at the University of Amsterdam and performed his PhD research in the field of theoretical biochemistry at the same university. During his PhD research, he studied the dynamics of glycolysis in yeast; he then switched to biomedical research in Leiden, where he studied lipid and glucose metabolism in mouse models. In 2008, Teusink became professor of Systems Biology and Integrative Bioinformatics at VU University Amsterdam. The focus is more in general on the use of constraint-optimization techniques to investigate the design principles of cellular physiology. The main organisms in the Teusink lab are currently *Lactoccocus lactis, Escherichia coli* and *Saccharomyces cerevisiae*. Although much of Teusink's work is fundamental in nature (he is a 2015 recipient of a prestigous Dutch VICI grant for scientific excellence), it is recognized by industry, as is evident from several public-private partnerships and the midterm career award he received in 2014 from the LABIP, the Lactic Acid Bacteria Industrial Platform.

**The regulation of cell motility through an excitable system**

**Pablo A. Iglesias**
**John Hopkins University**

**Abstract:** Recent years have demonstrated that the actin cytoskeleton and other signaling elements in motile cells have many of the hallmarks of an excitable medium, including the presence of propagating waves, a refractory period, as well as a threshold for activation. In this talk I show how these behaviors can be explained by the presence of a signal transduction excitable network that integrates a number of signals and coordinates actin polymerization. In this model, spontaneous triggering of the excitable network accounts for the random migration of unstimulated cells. Moreover, internal and external signals – both chemical and mechanical – bias excitability spatially, thus providing a means by which cell motility is directed towards spatial cues. We also show how the model predicts that the set point of the excitable system can be altered by changing the threshold. Moreover, these perturbations give rise to different migratory modes, including amoeboid, keratocyte-like and oscillatory movement. We demonstrate that our theoretical predictions can be recreated experimentally in motile amoeba.

**Bio:** Pablo A. Iglesias was born in Caracas, Venezuela. He received the B.A.Sc. degree in Engineering Science from the University of Toronto in 1987, and the Ph.D. degree in Control Engineering from Cambridge University in 1991. Since then he has been on the faculty of the Johns Hopkins University, where he is currently the Edward J. Schaefer Professor of Electrical Engineering. He also holds appointments in the Departments of Biomedical Engineering, and Applied Mathematics & Statistics as well as the Department of Cell Biology in the Johns Hopkins School of Medicine. He has had visiting appointments at Lund University (Automatic Control), The Weizmann Institute of Science (Mathematics), the California Institute of Technology (Control and Dynamical Systems), and the Max-Planck Institute for the Physics of Complex Systems in Dresden, Germany.

**Identification of Predictive Dynamic Models for Systems Biology**

**Jörg Stelling**
**ETH Zürich**

**Abstract:** Limited mechanistic knowledge, conflicting hypotheses, and still relatively scarce experimental data hamper the development of dynamic models for cellular networks. In addition, systems identification is often challenging because it concerns network topologies and parameters simultaneously. This talk will address open problems and new methods for systems identification at different levels of granularity, ideally leading to detailed mechanistic systems models. To derive a coarse-grained representation of network topologies, for example, to identify unknown natural inputs to signaling pathways, we discuss a probabilistic inference approach that relies on prototypic 'network motifs' and its application to nutrient signaling in yeast. When a basic model structure is inferred, but many mechanistic hypotheses are to be evaluated, the method of 'topological filtering' enables one to automatically generate a set of simple(r) models compatible with observational data; this approach allowed us to identify a single, highly plausible circuit topology in a stress signaling circuit by experiment-theory iterations. Finally, we will emphasize how network modularization and advanced numerical methods may achieve scalability of such identification approaches, which is critical for many real-world applications.

**Bio:** Jörg Stelling is a Professor for Computational Systems Biology at ETH Zurich. He studied Biotechnology at the Technical University of Braunschweig, before moving to the newly founded Max-Planck Institute for Dynamics of Complex Technical Systems, Magdeburg. He received his PhD in 2004 in systems dynamics and control from the Department of Mechanical Engineering, University of Stuttgart; his PhD thesis devised new methods for the analysis of robustness in complex biological networks. In 2005, he joined ETH Zurich's Computer Science Department before moving to the new ETH Department of Biosystems Science and Engineering in 2008. His current research interests are focused on the analysis and synthesis of biological networks using - and further developing - methods from systems theory and computer science. The highly interdisciplinary character of the research projects is reflected by an (international) network of collaborators from different disciplines.

# Program and Abstracts Sunday October 9

| 13:30-17:00 SuW1, G28 room 026 **Workshop: Optimization in Systems and Synthetic Biology: Concepts, Methods and Illustrative Examples** | 13:30-17:00 SuW2, G28 room 027 **Workshop: Kinetic and Optimization Based Models for Understanding the Regulation of Cellular Metabolism** |
|---|---|
| 18:00-20:00 SuRP, G28, **Welcome Reception** | |

### Technical Program for Sunday October 9, 2016

| SuW1 | G28 room 026 |
|---|---|
| **Optimization in Systems and Synthetic Biology: Concepts, Methods and Illustrative Examples** (Workshop) | |
| Chair: Otero, Irene | IIM-CSIC |
| Co-Chair: Balsa-Canto, Eva | CSIC |

| 13:30-17:00 | SuW1.1 |
|---|---|

*Optimization in Systems and Synthetic Biology: Concepts, Methods and Illustrative Examples*

| Otero-Muras, Irene | IIM-CSIC |
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| Balsa-Canto, Eva | IIM-CSIC |
| Banga, Julio R. | IIM-CSIC |

Mathematical optimization is at the core of many problems in systems biology and synthetics biology: i) as the underlying hypothesis for model development, ii) in model identification, iii) in the computation of optimal stimulation procedures to synthetically achieve a desired biological behaviour or iv) in the design of biological circuits. Most of these problems are usually formulated as (multi-)objective non- linear programming problems with dynamic and algebraic constraints whose solution requires of specific numerical tools. This workshop is organized in three modules: 1) Optimization basics 2) Optimization for the modelling in biological systems 3) Optimization for the design of biological circuits

More details:
http://www.fosbe2016.ovgu.de/Program/Workshops.html

| SuW2 | G28 room 027 |
|---|---|
| **Kinetic and Optimization--Based Models for Understanding the Regulation of Cellular Metabolism** (Workshop) | |
| Chair: Waldherr, Steffen | KU Leuven |

| 13:30-17:00 | SuW2.1 |
|---|---|

*Kinetic and Optimization--Based Models for Understanding the Regulation of Cellular Metabolism*

| Waldherr, Steffen | KU Leuven |
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| Bockmayr, Alexander | FU Berlin |
| Bruggeman, Frank | VU Amsterdam |
| Hatzimanikatis, Vassily | (EPFL) |

Constraint--based models formulated as an optimization problem are an established framework to describe the metabolic behaviour of living cells. In such models, the biochemical reaction fluxes are modelled as optimization variables subject to biophysical constraints, and an optimization problem with a biologically reasonable objective is solved to obtain model predictions for the values of the fluxes. As an alternative model class, kinetic models explicitly include the regulation of reactions in the model description. Classically, this requires that all regulations, e.g., allosteric, are known for the model construction. However, new modeling approaches soften this requirement, enabling the construction of genome-scale kinetic models similar in scope to established constraint-based models. The proposed workshop focusses specifically on the interface between kinetic and optimization-based models to understand the regulation of cellular metabolism in a dynamic context.

The workshop is being organized by the ROBUSTYEAST consortium. ROBUSTYEAST is an European research consortium funded under the ERA-Net for Applied Systems Biology (ERASysAPP) program with the goal of revealing the engineering principles for robustness of metabolism to nutrient dynamics with yeast as a model organism. The connection between optimization--based and kinetic models plays a crucial role in this, and the purpose of the workshop is to act as a platform for scientific exchange about the state of the art in this area between researchers within and outside the ROBUSTYEAST consortium. There is also an invited session in the main conference program by the same organizers which builds upon this workshop. Details will be provided when the conference program has been finalized. Workshop contributions

Aleksej Zelezniak, Francis Crick Institute, UK: "Metabolic network connectivity together with enzyme abundance as predictors of metabolite concentrations"

Ronan Fleming, University of Luxembourg, LU: "Variational kinetics: kinetic modelling based on variational analysis"

Ljubisa Miskovic, Georgios Fengos, Meric Ataman, Tuure Hameri, Vassily Hatzimanikatis, EPF Lausanne, CH: "Kinetic modeling of genome-scale metabolic networks of E. coli and yeast without sacrificing stoichiometric, thermodynamic and physiological constraints"

Panel discussion with the workshop contributors and the ROBUSTYEAST consortium about the connection between kinetic and optimization-based models.

More information:
http://www.fosbe2016.ovgu.de/Program/Workshops.html

# Program and Abstracts Monday October 10

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|---|---|
| 08:30-08:45 MoOP.    Nave, **Opening** | |
| 08:45-09:30 MoPMP, Nave, **Plenary Guy-Bart Stan** | |
| 09:30-10:00 MoKMP, Nave, **Keynote Robert S. Parker** | |
| 10:00-10:30 MoCMP, Nave, **Coffee Break** | |
| 10:30-12:10 MoM1,    Nave,<br>**Synthetic Biology** | 10:30-12:10 MoM2, Gallery<br>**Modelling – Health** |
| 12:10-14:10 MoPP,    Nave, **Poster Session I with Lunch** | |
| 14:10-15:00 MoPAP, Nave, **Public Plenary Frank Doyle** | |
| 15:10-15:40 MoKAP, Nave, **Keynote Rudi Gunawan** | |
| 15:40-16:10 MoCAP, Nave, **Coffee Break MA** | |
| 16:10-17:50 MoA1,    Nave<br>**Modelling–Microbial Systems** | 16:10-17:50 MoA2, Gallery<br>**Methods** |
| 17:50-19:30 MoCP, **Guided city walk and visit of the Magdeburg Cathedral** | |

| MoPMP | Nave |
|---|---|
| **Guy-Bart Stan** (Plenary Session) | |
| Chair: Balsa-Canto, Eva | CSIC |

| 08:45-09:30 | MoPMP.1 |
|---|---|

*Control Engineering Meets Synthetic Biology: Shared Resources and Feedback Considerations for Better Engineering of Bacterial Cells*

| Stan, Guy-Bart | Imperial College London |
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In this talk I will give an overview of some of our research activities in the "Control Engineering Synthetic Biology" group, where we focus our efforts on developing foundational forward-engineering methods to mathematically model, control, and experimentally implement synthetic gene circuits and cellular systems that aim at increasing the robustness, performance, and genetic stability of engineered cells. During the talk, I will propose some approaches to answer the following core questions in systems and synthetic biology:

How can we design taking into account shared resources to improve growth rates, genetic stability and robustness of synthetic biology systems?

How can we improve the dynamic performance (e.g. transient and response time) of synthetic biology systems?

How can we use cellular resources more efficiently to simultaneously improve growth rates and production yields?

In particular, I will present some recent work on the development of various de novo biomolecular feedback mechanisms in bacterial cells (mainly E. coli) that we use to answer the above questions. Our envisioned target applications for these novel designs include cell-based medicine, more efficient biosynthesis, and scale-up in synthetic biology and biotechnology.

| MoKMP | Nave |
|---|---|
| **Robert S. Parker** (Keynote Session) | |
| Chair: Klapa, Maria | Foundation for Res. and Tech |

| 09:30-10:00 | MoKMP.1 |
|---|---|

*A "Virtual Patient" Cohort and Mathematical Model of Glucose Dynamics in Critical Care*

| Knab, Timothy D. | Univ. of Pittsburgh |
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| Clermont, Gilles | Univ. of Pittsburgh |
| Parker, Robert S. | Univ. of Pittsburgh |

Stress hyperglycemia is common in critically ill patients and is strongly correlated with increased patient morbidity and mortality. Tight glucose control has been studied as a route to improving patient outcomes by attempting to maintain euglycemia in critical care patients. Unfortunately, glycemic variation associated with trauma or stress results from significant variations in insulin sensitivity and may also lead to significant hypoglycemia, which has been shown to be strongly correlated with patient mortality. To combat stress hyperglycemia, while taking care to avoid hypoglycemia, a number of systems including closed-loop control with continuous glucose monitoring have been proposed. We synthesize a mathematical model describing a virtual patient cohort, using clinical data obtained from a critical care unit at the University of Pittsburgh Medical Center, as a means to test these types of algorithms in silico. Virtual patients are primarily characterized by their insulin sensitivity and pancreatic insulin secretion profiles and exhibit time-varying trajectories consistent with physiological and clinical expectations. Overall, two patient groups result: (i) good sensitivity to insulin and stable insulin sensitivity trajectories (presumably returned to a healthy state); and (ii) depressed and variable sensitivity.

| MoM1 | Nave |
|---|---|
| **Synthetic Biology** (Regular Session) | |
| Chair: Stan, Guy-Bart | Imperial Coll |
| Co-Chair: di Bernardo, Diego | TIGEM |

| 10:30-10:50 | MoM1.1 |
|---|---|

*Dynamic Network Analysis Combined with Protein-Protein Interaction Knowledge Identified Short Feedback and Feed-Forward Circuits in Genetic Networks*

| Bar, Nadav S. | Norwegian Univ. of Science and Tech |
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| Jayavelu, Naresh D. | Univ. of Turku and Åbo Akademi Univ |

Genetic networks are complex with hundreds and thousands of interacting components. Feedback and feed-forward loops are well known to reduce noise of signals, increase robustness, introduce oscillations and bi-stability to the system. And yet, it is a challenge to extract information on regulation of individual genes in highly

interconnected networks, and to identify features such as feedback and feed-forward loops inside these. We aim to develop an algorithm to reveal such loops.

We combined network component analysis and time-series gene expression data with protein-protein databases (PPI) and extracted potential feedback and feed-forward candidates. We employed the network component analysis to predict temporal activities of transcription factors (TFs), and when we linked this information to existing static PPI databases, we revealed potential short regulatory circuits, with their positive or negative feature. We applied our method on large EGF and HRG data that we downloaded from available repositories and constructed an NCA-DEG-PPI network. We identified TFs that either suppress ongoing expression of downstream genes, or activate downstream genes that are responsible to counteract the stimuli. We also revealed genes that affect upstream genes by feedback loops. We verified several of these feedback circuits and revealed genes that potentially involved in gene regulation. This method becomes important as the amount of gene expression data increases, and it can be used to study regulation of genes in large networks.

| 10:50-11:10 | MoM1.2 |
|---|---|

*Control of Gene Expression for the Study of Neurodegenerative Disorders: A Proof-Of-Principle Experimental Study*

| Perrino, Giansimone | Univ. of Naples Federico II |
| Wilson, Cathal | TIGEM |
| Santorelli, Marco | TIGEM |
| di Bernardo, Diego | TIGEM, Univ. Naples Federico II |

Neurodegenerative disorders are characterised by the progressive disruption of specific neuronal population partly due to the formation of abnormal protein aggregates that interfere with normal cell functions. In Parkinson&apos;s disease, the role of abnormal alpha-synuclein protein aggregates in causing the disease is well established. Mutations in alpha-synuclein are known to cause familial Parkinson&apos;s disease. A quantitative understanding of the dynamics of alpha-synuclein protein aggregation in wild type and mutant form is however lacking. Here, we explore the feasibility of using a microfluidics-based platform for automatic control of protein expression from a galactose-inducible promoter in yeast, to model and study the human alpha-synuclein protein.

| 11:10-11:30 | MoM1.3 |
|---|---|

*A Multiobjective Optimization Approach to the Forward and Reverse Design of Biological Oscillators*

| Otero-Muras, Irene | IIM-CSIC |
| Banga, Julio R. | IIM-CSIC |

Although much has been learned concerning the sophisticated molecular mechanisms underlying biological oscillators, design principles linking structure and functional behaviour are not yet fully understood. Here we show the relevance of a multiobjective formulation in the design of biological oscillators (both in systems and synthetic biology applications), where the trade-offs among conflicting performance goals seem to play a crucial role.

| 11:30-11:50 | MoM1.4 |
|---|---|

*From a Discrete to Continuous Actuation for Improved Real-Time Control of Gene Expression in Mammalian Cells*

| Postiglione, Lorena | TIGEM, Univ. Naples Federico II |
| Santorelli, Marco | TIGEM, Univ. Naples Federico II |
| Tumaini, Barbara | TIGEM, Univ. Naples Federico II |
| di Bernardo, Diego | TIGEM, Univ. Naples Federico II |

Real-time automatic regulation of gene expression is a key technology for synthetic biology enabling, for example, synthetic circuit components to operate in an optimal range. We show that it is possible to regulate the expression of a reporter protein from the tetracycline-inducible promoter in a population of mammalian cells using principles from automatic control engineering. We demonstrate that the performance of the control experiments

improves by moving from a discrete to a continuous actuation. Our automated control platform is an innovative tool to enable dose-response studies of small molecules and investigation of gene dosage effects in disease.

| 11:50-12:10 | MoM1.5 |
|---|---|

*Bringing the Parts Together: Steps towards an In-Silico Protocell*

| Schneider, Eugenia | Max-Planck-Inst. for Dynamics of Complex Tech. Systems |
| Schweizer, Jakob | Max Planck Inst. for Dynamics of Complex Tech. Systems |
| Mangold, Michael | Max Planck Inst. for Dynamics of Complex Tech. Systems |

This article focuses on a system theoretic approach to synthetic biology, and in particular on the construction of a protocell model. The questions addressed here are: Which parts of functional modules are required to describe a protocell and which design methods are needed for self-replicating systems. We describe a model for an in-silico protocell that combines experimentally validated biological subsystems with theoretical studies.

| MoM2 | Gallery |
|---|---|
| **Modelling – Health** (Regular Session) | |
| Chair: Doyle, Francis | Harvard University |
| Co-Chair: Klapa, Maria | Foundation for Res. and Tech |

| 10:30-10:50 | MoM2.1 |
|---|---|

*A Simplified 2D Heart Model of the Wolff-Parkinson-White Syndrome*

| Zeile, Clemens | OvG Univ. of Magdeburg |
| Scholz, Eberhard | Univ. Hospital Heidelberg |
| Sager, Sebastian | OvG Univ. Magdeburg |

The enormous progress made in computational cardiac electrophysiology during the past decades has resulted in a diverse range of models and numerical methods. In general, researchers have elaborated highly complex and detailed simulators on the cell and tissue level. In contrast, there has been a lack of simplified whole-heart models that study specific heart arrhythmias. In this study, we approximate the electrophysiology of Wolff-Parkinson-White Syndrome with such a model. In order to reproduce the cardiac anomaly, we apply the so-called bidomain approach involving partial differential equations. Results show that the simulations are realistic, both in ECG generation and electric activation sequence. Our assessment of the model implementation takes into account parameter and geometry variation, which supports a realistic view of medical aspects. Our in silico analysis thus helps provide clear insights into the mechanisms of arrhythmias and associated ECG changes.

| 10:50-11:10 | MoM2.2 |
|---|---|

*Spatiotemporal Metabolic Modeling of a Chronic Wound Biofilm Consortium*

| Phalak, Poonam | Univ. of Massachusetts |
| Chen, Jin | Univ. of Massachusetts |
| Carlson, Ross P. | Montana State University |
| Henson, Michael A. | Univ. of Massachusetts |

Chronic wounds are often colonized by consortia comprised of different bacterial species growing as biofilms on a complex mixture of wound exudate. The spatial organization of biofilm consortia cause bacteria to exhibit phenotypes distinct from planktonic growth and often render the application of antibacterial compounds ineffective. We developed a spatiotemporal model to analyze the multispecies metabolism of a biofilm consortium comprised of two common chronic wound isolates: the aerobe *Pseudomonas aeruginosa* and the facultative anaerobe *Staphylococcus aureus*. By combining genome-scale metabolic reconstructions with partial differential equations for metabolite diffusion, the model was able to provide both temporal and spatial

predictions with genome-scale resolution. The model was used to analyze the metabolic differences between single species and multispecies biofilms and to demonstrate the tendency of the two bacteria to spatially partition due to nutrient gradients. The model predicted that *S. aureus* would dominant throughout the biofilm, especially in the anaerobic region where *P. aeruginosa* had very low growth rates. Lactate secreted by *S. aureus* and consumed by both species was predicted to further diminish *P. aeruginosa* competitiveness due to its lower cell densities. Lysis of *S. aureus* by inhibitors secreted from *P. aeruginosa* was predicted to enhance spatial partitioning of the two species and to substantially enhance the competitiveness of *P. aeruginosa* in partially aerobic regions of the biofilm interior.

| 11:10-11:30 | MoM2.3 |
|---|---|

*Coupling Cellular Phenotype and Mechanics to Understand Extracellular Matrix Formation and Homeostasis in Osteoarthritis*

| Sunkara, Vikram | Freie Univ. Berlin, ZIB |
| von Kleist, Max | Freie Univ. Berlin |

Osteoarthritis of the knee is a common degenerative disease during aging. It is typically caused by articular cartilage degeneration. Cartilage, which is located between bone surfaces, is a viscoelastic material aiming to absorb, redirect and transmit mechanical forces during movement. Without the cartilages&apos; buffering capacity, bones come into direct contact inducing severe pain up to the stage where affected individuals loose mobility. The mechanisms of cartilage remodeling are poorly understood, and there is currently no effective method to reconstitute damaged cartilage. Cartilage consists of extracellular matrix (ECM) and a low density of cells (chondrocytes), which generate matrix proteins. The composition of the matrix gives the cartilage specific viscoelastic properties, which are sensed by chondrocytes feeding back on ECM remodeling. The aim of this study is to build a mathematical model that couples mechanical ECM properties with chondrocyte phenotype in the upkeep of cartilage homeostasis. We model the viscoelastic properties of the cartilage in terms of a linear Kelvin-Voigt model, where the dampening ratio feeds back on the phenotypic switching behaviour in chondrocytes. The chondrocytes, depending on their phenotypic state, may either produce proteoglycans or collagens or both, which alters the viscoelastic properties of the cartilage. We formulate a coupled system of equations integrating mechano-sensitive phenotypic switching behaviour of chondrocytes with respect to ECM remodelling. We define cartilage homeostasis as the fixed point of the derived systems of equations. Using this framework we can reproduce the long term changes in cartilage composition during aging.

| 11:30-11:50 | MoM2.4 |
|---|---|

*Parameter Estimation for Leukocyte Dynamics after Chemotherapy*

| Rinke, Kristine | OvG Univ. Magdeburg |
| Jost, Felix | OvG Univ. Magdeburg |
| Findeisen, Rolf | OvG Univ. Magdeburg |
| Fischer, Thomas | OvG Univ. Hospital Magdeburg |
| Bartsch, Rainer | OvG Univ. Hospital Magdeburg |
| Schalk, Enrico | OvG Univ. Hospital Magdeburg |
| Sager, Sebastian | OvG Univ. Magdeburg |

Leukopenia is one of the most harmful side effects during chemotherapy treatment, since leukocytes (L) are crucial in protecting patients against bacteria and fungi. A personalized mathematical model of dynamics of L would allow a glimpse into the future and the initiation of tailored countermeasures. We propose such a mathematical model and calibrate it based on a parameter estimation with real world data. For our study we used data of L during and after consolidation chemotherapy treatment (cytarabine) of six patients contracting acute myeloid leukemia. We compare two different ways to treat the unknown initial values of the system of ordinary differential equations, discuss patient-specificity of parameter values, and different scalings of the least squares formulation. These three comparisons are necessary

considerations for all modeling approaches to biomedicine, and have thus a methodological scope beyond the specific case of leukopenia. In summary, we show that our approach is able to simulate L dynamics in response to chemotherapy treatment and allows to take patient-specific characteristics into account.

| 11:50-12:10 | MoM2.5 |
|---|---|

*Invariant Based Control of Induction and Maintenance Phases for Anesthesia*

| Fiacchini, Mirko | GIPSA-Lab, CNRS |
| Queinnec, Isabelle | LAAS-CNRS |
| Tarbouriech, Sophie | LAAS-CNRS |
| Mazerolles, Michel | CHU Toulouse |

Set theory and invariant sets are the key ingredients used in this paper to address the control problem of general anesthesia. Both the induction phase, corresponding to the administration of an open-loop bolus dose, and the maintenance phase of the depth of hypnosis during the surgical operation are considered. The obtained control results to emulate the multi-phase control law used in practice.

| **MoPP** | Nave |
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**Lunch + Poster Session I** (Poster Session)

| 12:10-14:10 | MoPP.1 |
|---|---|

*Normalization of Western Blot Data Affects the Statistics of Estimators*

| Thomaseth, Caterina | Univ. of Stuttgart |
| Radde, Nicole | Univ. of Stuttgart |

This study elaborates on the normalization of data from Western blot experiments and its impact on parameter estimation. Western blot data have to be preprocessed appropriately in order to enable comparison across different replicates. This includes a two step normalization procedure, in which the raw signals are normalized to a loading control and additionally to a reference condition. If the signals themselves are normally distributed, the normalized data are described by ratios of normal distributions, which have some peculiarities that can complicate further analysis such as parameter estimation for biochemical Network reconstruction. Here we shortly recapitulate some properties of these ratio distributions and conditions for various approximations that facilitate further analysis. We illustrate results on a case study in which Western blot data are used to infer the fold change in a knockdown experiment.

| 12:10-14:10 | MoPP.2 |
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*New Concepts for Evaluating the Performance of Computational Methods*

| Kreutz, Clemens | Albert-Ludwigs-Univ. Freiburg |

Research in Systems Biology is currently entering a new era. After a decade characterized by adopting existing experimental protocols and theoretical approaches to the requirements of Systems Biology, there is now a variety of tools and approaches available. However, many statistical and modeling concepts are not well-tested in application settings and their applicability is often seriously delimited. Therefore, a major challenge for the transfer of theoretical approaches to applications is the assessment and optimization of the methods&apos; performance for supporting experimental research.

In this paper, new concepts for assessing methods which were developed for analyzing experimental data in the context of systems biology will be introduced. Some ideas are illustrated by evaluating the impact of the logarithmic transformation for parameter estimation. A strong benefit of the log-transformation was observed for five different ODE models. The suggested framework enables less biased and more reliable and valid assessment and comparison of competing approaches than currently performed in the literature. The presented concepts could serve as basis for developing decision guidelines for optimal

selection of analysis methods and thereby enhancing the transfer of systems biological procedures and reverse engineering methods to industrial applications like drug development.

| 12:10-14:10 | MoPP.3 |
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*A Constrained NMF Approach to Analyze Quantitative Metagenomic Data*

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| Raguideau, Sébastien | MaIAGE, INRA, Univ. Paris-Saclay |
| Laroche, Béatrice | MaIAGE, INRA, Univ. Paris-Saclay |
| Leclerc, Marion | Micalis, INRA, Univ. Paris-Saclay |
| Plancade, Sandra | MaIAGE, INRA, Univ. Paris-Saclay |

In this paper, we propose a new method for inferring the metabolic potential of microbial ecosystems based on gene frequencies generated from shotgun metagenomic data. Our approach is based on Non-Negative Matrix Factorization with constraints accounting for prior biological knowledge of bacterial metabolism. The problem is solved using efficient accelerated projected gradient methods. The approach is illustrated on a toy model and on real data on fiber metabolism by the gut microbiota in humans. We show how this approach leads to the inference of biologically relevant gene clusters.

| 12:10-14:10 | MoPP.4 |
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*Parameter Identification in Synthetic Biological Circuits Using Multi-Objective Optimization*

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| Boada, Yadira | Univ. Pol. De Valencia |
| Vignoni, Alejandro | Max Planck Inst. of Molecular Cell Biology and Genetics |
| Reynoso-Meza, Gilberto | Pontificia Univ. Católica De Paraná |
| Picó, Jesús | Univ. Pol. De Valencia |

Synthetic biology exploits the mathematical modeling of synthetic circuits both to predict the behavior of the designed synthetic devices, and to help on the selection of their biological components. The increasing complexity of the circuits being designed requires performing approximations and model reductions to get handy models. Parameter estimation in these models remains a challenging problem that has usually been addressed by optimizing the weighted combination of different prediction errors to obtain a single solution. The single-objective approach is inadequate to incorporate different kinds of experiments, and to identify parameters for an ensemble of biological circuit models.

We present a methodology based on multi-objective optimization to perform parameter estimation that can fully harness to ensembles of local models for biological circuits. The methodology uses a global multi-objective evolutionary algorithm and a multi-criteria decision making strategy to select the most suitable solutions. Our approach finds an approximation to the Pareto optimal set of model parameters that correspond to each experimental scenario. Then, the Pareto set was clustered according to the experimental scenarios. This, in turn, allows to analyze the sensitivity of model parameters for different scenarios. Finally, we show the methodology applicability through the case study of a genetic incoherent feed-forward circuit, under different concentrations of the inducer input signal.

| 12:10-14:10 | MoPP.5 |
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*A Parallel Modelling Algorithm for Simulating Calcium Release in Cells*

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| Stoddard, Jeremy G. | Univ. of Newcastle |
| Welsh, James S. | Univ. of Newcastle |
| Laver, Derek R. | Univ. of Newcastle |

Using a spatially discretised model structure to represent the behaviour of calcium release sites in a cell, this paper presents a parallel solution algorithm which treats each release site as an

independent sub-system, and manages inter-site data communication on a global timestep. When compared to the equivalent single-thread solution algorithm, the parallel method features a negligible reduction in accuracy, and improves computation time scaling from a quadratic, $O(n^2)$ to a linear, $O(n)$, with respect to the number of release sites, $n$, in the model.

| 12:10-14:10 | MoPP.6 |
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*Preconditioned Metropolis Sampling As a Strategy to Improve Efficiency in Posterior Exploration*

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| Engblom, Stefan | Uppsala Univ. |
| Sunkara, Vikram | FU Berlin, ZIB |

In the low copy number regime, the dynamics of chemically reacting systems is accurately modeled as a continuous-time Markov chain and the associated probability density obeys the chemical master equation. Parameter inference in such models is very challenging for various reasons: large levels of noise implies that large amount of data is required for identification, the presence of transient phases may shadow subsets of the parameters, and accurate likelihood estimation requires the solutions to master equations. The latter is itself a computational very challenging problem and although many approximate computational methods have been proposed previously, the final implied accuracy in estimated rate parameters is difficult to assess.

In this paper we look at the problem from the perspective of the Markov chain Monte Carlo method. Assuming the existence of a practically exact, but expensive, master equations solver, together with a cheaper, approximate alternative, we pick up the idea of preconditioned Metropolis sampling. Here the solutions of full master equations almost always imply an accepted step in the Markov chain, and consequently, step rejections are much cheaper. We investigate the properties of this technique theoretically and via illustrative examples. Whenever a suitable preconditioner is available, large savings in computational times are possible while the accuracy in deduced parameters is identical to using the exact likelihood.

| 12:10-14:10 | MoPP.7 |
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*Integrating Classifiers across Datasets Improves Consistency of Biomarker Predictions for Sepsis*

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| Saraiva, João Pedro | Hans Knöll Inst. Centre for Sepsis Control and Care |
| Oswald, Marcus | Hans Knöll Inst. Centre for Sepsis Control and Care |
| Biering, Antje | Hans Knöll Inst. Centre for Sepsis Control and Care |
| Assman, Cora | Septomics Res. Centre, Jena Univ. Hospital |
| Klassert, Tilman | Septomics Res. Centre, Jena Univ. Hospital |
| Blaess, Markus | Centre for Sepsis Control and Care, Jena Univ. Hospital |
| Czakai, Kristin | Univ. Hospital Würzburg |
| Claus, Ralf | Centre for Sepsis Control and Care, Jena Univ. Hospital |
| Löffler, Jürgen | Univ. Hospital Würzburg |
| Slevogt, Hortense | Septomics Res. Center, Jena Univ. Hospital |
| König, Rainer | Hans Knöll Inst. Centre for Sepsis Control and Care |

Systemic infection can cause multiple organ failure leading to severe sepsis and often death. Hence, early diagnosis is mandatory. Several transcriptomics studies were performed resulting in biomarker lists for diagnosis. This lists, however are very inconsistent. We developed Mixed Integer Linear Programming based classifiers (Support Vector Machines), trained them separately with different datasets, and combined them by constraining them to use the same sets of features. Strikingly, this

improved the consistency of the predicted biomarkers across datasets by 42%. Our approach is generic, it enabled to integrate diverse datasets and, with this, improved the consistency of predictions.

| 12:10-14:10 | MoPP.8 |
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*A Curvilinear Model Approach: Actin Cortex Clustering Due to ATP-Induced Myosin Pull*

| Wölfer, Christian | Max Planck Inst. for Dynamics of Complex Tech. Systems |
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| Vogel, Sven K. | Max Planck Inst. of Biochemistry |
| Mangold, Michael | Max Planck Inst. for Dynamics of Complex Tech. Systems |

The actomyosin cortex is involved in a range of many cellular processes like cell division, motility or shaping. To obtain this variety of functionalities the membrane-bound actin mesh has to be reconstituted by the motor protein myosin. But little is known about the underlying mechanism, which control the different tasks. An underlying in vitro study of a synthetic actomyosin cortex has shown that the cortex organizes into spatial clusters for certain ATP concentrations. Here we develop a curvilinear model that captures the viscoelastic material behavior and the kinetics of the myosin cross bridge. Further, we suggest a formulation for the active contractile stress produced by the motor protein myosin. We demonstrate that the spatial pattern generated by the curvilinear model is consistent with the experimental observations, including mesh clustering due to contractile forces and an absence of contraction for low and high ATP concentrations. Additionally we show that the cluster positioning can be tuned by the ATP-gradient.

| 12:10-14:10 | MoPP.9 |
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*Optimising Time-Series Experimental Design for Modelling of Circadian Rhythms: The Value of Transient Data*

| Mombaerts, Laurent | Univ. of Luxembourg |
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| Mauroy, Alexandre | Univ. of Luxembourg |
| Goncalves, Jorge M. | Univ. of Luxembourg |

Circadian clocks consist of complex networks that coordinate the daily cycle of most organisms. In light/dark cycles, the clock is synchronized (or entrained) by the environment, which corresponds to a constant rephasing of the oscillations and leads to a steady state regime. Some circadian clocks are endogenous oscillators with rhythms of about 24-hours that persist in constant light or constant darkness. This operating mechanism with and without entrainment provides flexibility and robustness to the clock against perturbations. Most of the clock-oriented experiments are performed under constant photoperiodic regime, overlooking the transitory regime that takes place between light/dark cycles and constant light or darkness. This paper provides a comparative analysis of the informative potential of the transient time-series data with the other regimes for clock modelling. Realistic data were simulated from 2 experimentally validated plant circadian clock models and sliced into several time windows. These windows represent the different regimes that take place before, meanwhile and after the switch to constant light. Then, a network inference tool was used over each window and its capability of retrieving the ground-truth of the network was compared for each window. The results suggest that including the transient data to the network inference technique significally improves its performance.

| 12:10-14:10 | MoPP.10 |
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*Validation Methods for Population Models of Gene Expression Dynamics*

| González-Vargas, Andrés M. | Univ. Autónoma De Occidente |
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| Cinquemani, Eugenio | INRIA Grenoble - Rhône-Alpes |
| Ferrari-Trecate, Giancarlo | Univ. Degli Studi Di Pavia |

The advent of experimental techniques for the time-course monitoring of gene expression at the single-cell level has paved the way to the model-based study of gene expression variability within- an across-cells. A number of approaches to the inference of models accounting for variability of gene expression over isogenic cell populations have been developed and applied to real-world scenarios. The development of a systematic approach for the validation of population models is however lagging behind, and accuracy of the models obtained is often assessed on a semi-empirical basis. In this paper we study the problem of validating models of gene network dynamics for cell populations, providing statistical tools for qualitative and quantitative model validation and comparison, and guidelines for their application and interpretation based on a real biological case study.

| 12:10-14:10 | MoPP.11 |
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*Using Optimal Control to Understand Complex Metabolic Pathways*

| Tsiantis, Nikolaos | IIM-CSIC |
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| Banga, Julio R. | IIM-CSIC |

The idea of predicting biological behaviour from first-principles is extremely appealing. A promising approach is to exploit optimality principles that can be justified from an evolutionary perspective (Sutherland,2005). In the context of the cell, several researchers have tried to explain the dynamics of simple metabolic pathways exploiting optimality principles in combination with dynamic models. For example, Klipp et al (2002) analysed dynamics of gene expression in small metabolic models, assuming that cells have developed optimal adaptation strategies. Most of these works have considered rather simplified representations, such as small linear pathways or networks with a single branching point.

Here we consider the extension of this approach to more realistic scenarios, i.e. biochemical pathways of arbitrary size and structure. We first show that exploiting optimality principles for these networks poses great challenges due to the complexity of the associated dynamic optimization problems. Second, in order to surmount such challenges, we present a computational framework based on multicriteria optimal control theory, and which has been designed with scalability and efficiency in mind, extending several recent methods (Hijas-Liste et al,2014). This framework includes mechanisms to avoid common pitfalls, such as local optima, unstable solutions or excessive computation time.

We illustrate its performance with several case studies considering the central carbon metabolism of S. cerevisiae and B. subtilis. In particular, we consider metabolic dynamics during nutrient shift experiments. We show how multi-objective optimal control can be used to predict temporal profiles of enzyme activation and metabolite concentrations. Further, the multicriteria approach allow us to consider general cost/benefit trade-offs that have been likely favored by evolution. We discuss the potential application of this computational framework to large-scale kinetic models of metabolism and signal transduction.

References: Hijas-Liste et al(2014), BMC Systems Biology,8:1. Klipp et al(2002) Eur. J. Biochem. 269:5406–5413. Sutherland, W.J.(2005) Nature 435(7042),569-569.

| 12:10-14:10 | MoPP.12 |
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*Parameter Estimation in Models of Biological Oscillators: Pitfalls and Solutions*

| Pitt, Jake Alan | BioProcess Engineering Group, IIM-CSIC, 36208 Vigo (Spain) |
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| Banga, Julio R. | IIM-CSIC |

Dynamic modelling is a central element in the systems biology approach to understand complex biosystems. Here we consider the problem of parameter estimation in models of biological oscillators described by deterministic nonlinear ordinary differential equations. These problems can be extremely challenging due to several common pitfalls: (i) a lack of prior knowledge about parameters (i.e. massive search spaces), (ii) convergence to local optima (due to multimodality of the cost function) and (iii) over-fitting (fitting the noise instead of the signal) [1]. As a consequence, the use of standard estimation methods (such as gradient-based local ones) will very often result in wrong solutions. Overfitting can be particularly problematic, since it produces very good calibrations, giving the impression of an excellent result.

However, overfitted models have poor predictive power.

Here we present several ideas to overcome these pitfalls. Firstly we use sampling strategies to systematically tighten the parameter bounds, reducing the search space. Secondly, we use efficient global optimization to avoid convergence to local solutions. Thirdly we use advanced regularization techniques to fight overfitting, extending the methods discussed in [2]. This novel combined approach is evaluated considering several difficult case studies, including the calibration of Goodwin and Fitz-Hugh–Nagumo oscillators. We show how local gradient-based approaches even if used in multi-start fashion, are not able to avoid the above mentioned pitfalls. In contrast our approach results in more efficient estimations (thanks to the bounding strategy) which are able to escape convergence to local optima (thanks to the global optimization approach). Further, the use of regularization allow us to avoid overfitting, resulting in more generalizable calibrated models (i.e. greater predictive power).

References [1] Villaverde, A.F. and J.R. Banga (2014) J. Royal Soc. Interface 11(91):20130505. [2] Gábor, A. and J. R. Banga (2015) BMC Systems Biology, 9:74.

| 12:10-14:10 | MoPP.13 |
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*Modeling, Optimization and Control of Biological Systems with AMIGO2*

| Balsa-Canto, Eva | CSIC |
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| Henriques, David | IIM-CSIC |
| Gabor, Attila | Mta Sztaki |
| Banga, Julio R. | IIM-CSIC |

Mathematical optimization plays a critical role in understanding, modeling, designing and controlling biological systems. Most of the problems can be posed as multi-objective nonlinear optimization problems with nonlinear dynamic constraints. Their solution requires the combination of several numerical approaches, such as the control vector parameterization method, a boundary or initial value problem solver and a suitable optimizer. Nevertheless, and despite their interest in the context of biological systems, no current tool allows the systematic solution of all such problems. This work presents a multiplatform MATLAB-based environment, AMIGO2, intended to offer state-of-the-art numerical solutions to handle mathematical optimization problems in systems and synthetic biology.

| 12:10-14:10 | MoPP.14 |
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*Identifiability Analysis of Dynamic Models in Systems Biology: A Combined Structural, Practical, and Graphical Approach*

| Fernández Villaverde, Alejandro | Univ. De Vigo |
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| Gabor, Attila | Mta Sztaki |
| Banga, Julio R. | IIM-CSIC |

The study of parameter identifiability can be approached from two points of view. Symmetries in the model equations may lead to structurally unidentifiable parameters, whose values cannot be uniquely determined even with perfect data. Additionally, a structurally identifiable parameter may be practically unidentifiable: its estimate will be highly uncertain due to data limitations. Any efforts invested in estimating unidentifiable parameters will fail, and may lead to wrong model predictions. Furthermore, if structural unidentifiability is mistaken for practical unidentifiability, the error may lead to trying to overcome it by investing additional efforts in new experiments, which will be sterile.

Here we show how to assess the identifiability of nonlinear dynamic models from structural and practical viewpoints, applying recently developed techniques. To analyze structural identifiability (SI) we consider the model parameters as state variables with zero dynamics and recast the study of identifiability as a generalization of (nonlinear) observability. By calculating the rank of the resulting generalized observability-identifiability matrix we determine the subset of SI parameters. Then we use a collinearity index and integer optimization to find the largest subset of practically identifiable parameters. Finally, we show these results on a network diagram of the system, which allows visualizing groups of identifiable/unidentifiable parameters and their relationships.

We use as case study the gene network of the circadian clock in *Arabidopsis thaliana* with 28 parameters. We report that it is structurally unidentifiable and show how to make it identifiable by fixing several parameters (e.g. the 5 constants marked as orange dots in the figure; the remaining parameters are in green). Then we study its practical identifiability, finding several alternative subsets of practically identifiable parameters. The procedure allows modelers to detect parts that need reformulation, and assist experimentalists in the design of new experiments.

| 12:10-14:10 | MoPP.15 |
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*Letting Data Choose the 13C Flux Model: On How to Do It and the Consequences of (not) Doing It*

| Theorell, Axel | IBG-1: Biotechnology, Forschungszentrum Jülich |
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| Leweke, Samuel | IBG-1: Biotechnology, Forschungszentrum Jülich |
| Wiechert, Wolfgang | IBG-1: Biotechnology, Forschungszentrum Jülich |
| Rocco, Andrea | Faculty of Health and Medical Sciences, Univ. of Surrey |
| McFadden, Johnjoe | Faculty of Health and Medical Sciences, Univ. of Surrey |
| Katharina, Nöh | Forschungszentrum Jülich |

Bayesian posterior probabilities can be used to compare computational models, guiding the modeling process towards an adequate model size. Aiming at model selection, application of Bayesian posterior probabilities in $^{13}$C metabolic flux analysis ($^{13}$C MFA)is challenging due to the high dimensionality of the underlying mathematical models. In this contribution we adapt a Markov Chain Monte Carlo approach to calculate the posterior probability of models in $^{13}$C MFA and showcase this using a realistic *E. coli* network.

| 12:10-14:10 | MoPP.16 |
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*Identification of Patient Cystic Fibrosis Population Parameters Via Probabilistic and Profile Likelihood Estimates*

| Markovetz, Matthew | Univ. of Pittsburgh |
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| Corcoran, Timothy | Univ. of Pittsburgh |
| Pilewski, Joseph | Univ. of Pittsburgh |
| Parker, Robert S. | Univ. of Pittsburgh |

Model parameter and structure estimation are fundamental challenges in systems medicine and, more generally, in systems biology. Determining the identifiability of model parameters, given experimental data, justifies structural choices in the model and can be used to decrease the parameter search space. Furthermore, identifiability analyses often provide population-scale information in the form of parameter likelihood estimates. Herein we utilize and compare two such analysis methodologies in the estimation of lung clearance model parameters: Markov Chain Monte Carlo search and the Profile Likelihood. We discuss the qualitative (and often quantitative) agreement of these methods and compare their performance in estimating patient parameters in a continuous inhalation of hypertonic saline trial with the objectives of improving mucociliary clearance and reducing airway absorptivity in patients with Cystic Fibrosis. We also use resultant parameter estimates, particularly the deposition parameters, to extend the analysis of the null clinical result.

| 12:10-14:10 | MoPP.17 |
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*Workflow for Identification of Enzyme-Kinetic Networks*

Spiess, Antje                                    TU Braunschweig

Characterization of enzyme kinetics is used in both enzymology and biochemical engineering, but with different objectives. We embedded enzyme kinetic model identification into a workflow consisting of derivation of kinetic equations, identifiability analysis, incremental parameter estimation, and optimal experimental design that allowed us to retrieve mechanistic kinetic models that are applicable both for protein engineering and for reactor design.

| 12:10-14:10 | MoPP.18 |
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*Using Rxncon to Model Signal Transduction at the Resolution of Empirical Data*

Krantz, Marcus                                    Humboldt-Univ. Zu Berlin

Modelling cellular signalling has proven difficult due to the combinatorial complexity and sparse data. Signalling components can have many interaction partners and modifications that can be combined into many distinct configurations – or microstates. This makes it difficult to precisely represent the empirical knowledge: First, the number of microstates increases combinatorial with the number of protein modifications. Second, the empirical data typically have a much lower resolution than these microstates. These issues are relatively benign for small models but devastating in larger models, seemingly blocking the progress towards genome scale signalling models. Consequently, we need a fundamentally different approach to build comprehensive models of signal transduction. To this end, we developed rxncon, the reaction-contingency approach. In rxncon, the network is defined in terms of reactions as well as constraints, or contingencies, on these reactions. Both reactions and contingencies are defined in terms of elemental states – i.e. indivisible properties, such as specific modifications, without further context – which allow them to be defined at variable resolution by combining elemental states. Hence, the rxncon approach is closely related to rule based modelling, and a rxncon network can be compiled into a rule based model in the BioNetGen language. The rxncon language is designed for large scale network reconstruction, and can be used to faithfully formalise empirical data while largely avoiding the combinatorial complexity. This rxncon network defines a formal model that can be simulated with rule based or Boolean logic, which in turn can be used for network validation. Taken together, the rxncon approach can be used to build, validate and simulate large signalling networks at the resolution of empirical data. Consequently, it opens up for comprehensive – in terms of both scope and molecular detail – models of signal transduction.

| 12:10-14:10 | MoPP.19 |
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*Stochastic Multiscale Modeling of Influenza Virus Production in Cell Cultures*

| Rüdiger, Daniel | Max Planck Inst. for Dynamics of Complex Tech. Systems |
| Heldt, Stefan | Max Planck Inst. for Dynamics of Complex Tech. Systems |
| Reichl, Udo | Max Planck Inst. for Dynamics of Complex Tech |

Stochastic models allow the description of systems in which critical components present in small numbers exert a tremendous influence on the overall process. Here we introduce a stochastic multiscale model of influenza virus production in cell cultures and examine differences between stochastic and deterministic simulation as well as approaches to counter increasing computational costs involving simulations of highly structured models for a large number of individual cells. Therefore, we employed an integrated modeling approach which combines a mechanistic model of intracellular replication dynamics with the infection dynamics on the population level. In this work we investigate if the consideration of stochastic fluctuations can explain cell-to-cell heterogeneity identified experimentally in single-cell infections (Heldt & Kupke et al., 2015). In addition, we examine whether variable time delays in onset of virus increase during cell culture-derived influenza virus production is due to

stochasticity of low multiplicity infections. Furthermore, we study the simulation of this model with a focus on reducing computational effort to support parameter estimation. To this end, we employ Gillespie algorithm-based methods (Gillespie, 2007) and a direct numerical solution of the chemical master equation (Kazeev et al., 2014). Our results demonstrate that especially during the early phase of influenza virus replication in cell cultures stochastic fluctuations can considerably affect the time course of production. Furthermore, we show that stochastic simulation of complex biological system can be improved substantially employing novel mathematical approaches.

REFERENCES Gillespie, D. T. (2007). Stochastic simulation of chemical kinetics. Annual Review of Physical Chemistry, 58, 35-55. Heldt, F. S., Kupke, S. Y., Dorl, S., Frensing, T., and Reichl, U. (2015). Single-cell analysis and stochastic modelling unveil large cell-to-cell variability in influenza A virus infection. Nature Communications, 6:8938. doi:10.1038/ncomms9938. Kazeev, V., Khammash, M., Nip, M., and Schwab, C. (2014). Direct solution of the chemical master equation using quantized tensor trains. PLOS Computational Biology, 10(3), e1003359.

| 12:10-14:10 | MoPP.20 |
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*Integration of Single Cell and Population Data for Model Parametrization of the Yeast Cell Cycle*

| Schlichting, Julia Katharina | Humboldt-Univ. Berlin |
| Amoussouvi, Aouefa | Humboldt Univ. Berlin |
| Schreiber, Gabriele | Humboldt-Univ. Berlin |
| Klipp, Edda | Humboldt-Univ. Berlin |

Saccharomyces cerevisiae is one of the most famous model organism in systems biology to study the mitotic cell cycle in eucaryotic cells. The cell cycle comprises the interphase and the M phase. The interphase includes two gap phases (G1 and G2), responsible for growth and preparation of the subsequent cell division, and a synthesis phase (S), responsible for DNA replication. The M phase consists of the nuclear division (mitosis) and the cytoplasmic devision (cytokinesis). START is a control point regulating the G1 to S phase transition. Cyclins, CDKs (cyclin-dependent kinases) and CKI (CDK inhibitors) are typical proteins involved in cell cycle control. The cyclins bind to their corresponding CDKs to form active complexes. The CKIs inhibit these complexes. We measured the number of gene transcripts in single cells as well as the transcriptional variability in populations for SIC1, CLN2 and CLB5 by smRNA-FISH. The absolut number of mRNA molecules of unsynchronized cells can be assigned to the cell cycle phases by using morphological markers. This measurement yields mRNA distributions per cell cycle phase. We quantified protein numbers for Sic1, Cln2 and Clb5 by generating Western blot data. Contrary to the smRNA-FISH data, the Western blot data are population data of synchronized cells. The number of proteins is a relative measure and given as time course over the cell cycle. Therefore these both methods are not directly comparable. In the present work we combine both data types to parameterize the transcriptional and translational part of a START network based on a stochastic modelling approach. We are using the ODE system describing the mean number of molecules to estimate the parameters with a maximum likelihood estimation. The optimization process is highly sensitive to the initial conditions. The algorithm failed to converge for many initial values. This is why the question of the best fit is obvious. To overcome this problem we scan a set of 1000 different initial conditions to identify local optima and the potential global optimum. The parameter distributions of all fits lead to the vicinity of the global optimum are narrow. They are therefore a good starting point for further analysis.

| 12:10-14:10 | MoPP.21 |
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*Modelling Carotene Desaturation Via Phytoene Desaturase (PDS)*

| Fehling-Kaschek, Mirjam | Univ. of Freiburg |
| Koschmieder, Julian | Univ. of Freiburg |
| Beyer, Peter | Univ. of Freiburg |
| Timmer, Jens | Univ. of Freiburg |

Carotenes play a major role in the coloration and photosynthesis of plants. In this project, the transformation of phytoene via the intermediate phytofluene to zeta-carotene by the enzyme PDS is investigated. Phytoene is a hydrocarbon containing 40 carbon atoms that are arranged in two symmetrical half sides. PDS can introduce a double-bond to either half side of phytoene (desaturation), forming the intermediate phytofluene. The end product zeta-carotene is formed by the same PDS desaturation on the second half side.

A mathematical model based on ordinary differential equations is used to describe the desaturation process. The substrate (phytoene or phytofluene) binding to the enzyme PDS and the following product formation are modeled by mass action kinetics. Further processes included in the model are the re-oxidation and inactivation of the enzyme. Experimental observation of PDS homo-oligomers motivates cooperative intermediate-enzyme binding. Time-resolved data of phytoene, phytofluene and zeta-carotene concentrations is employed to determine model parameters by maximum-likelihood estimation. Data for different initial phytoene or phytofluene concentrations as well as for a mutant enzyme is used to calibrate the model.

The different aspects of phytoene-, phytofluene- and zeta-carotene dynamics are accurately captured by the mathematical model. It turns out that the inactivation of the enzyme is the key explanation for the observed transient dynamics. Furthermore, the cooperativity incorporated by the PDS dimers is crucial to describe the different experimental conditions jointly.

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| 12:10-14:10 | MoPP.22 |
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*A Reaction-Diffusion Model to Describe Listeria Monocytogenes Biofilms Life Cycle*

| Balsa-Canto, Eva | CSIC |
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| Vilas, Carlos | Inst. De Investigacions Mariñas |
| Mosquera-Fernandez, Maruxa | IIM-CSIC |
| Briandet, Romain | INRA |
| Cabo, Marta L. | IIM-CSIC |

This work combines quantitative microscopy image analysis and mathematical modeling to understand and explain the life cycle of L1A1 {it L. monocytogenes} biofilms. Confocal laser microscopy and quantitative image analysis were used to characterize the structure of biofilms. The two-dimensional analysis of the images revealed that L1A1 biofilms are rather flat; while a three-dimensional analysis was used to compute the biofilm thickness through time. A reaction-diffusion model was then proposed to undestand and explain L1A1 biofilm life cycle in batch culture. The model describes biomass and nutrients evolution incorporating several mechanisms such as biomass growth and spread, nutrients diffusion and consumption, and microbial decay. Unknown model parameters were estimated by means of data fitting. Remarkably the mechanisms of microbial decay are critical to get satisfactory model predictions.

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| 12:10-14:10 | MoPP.23 |
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*Parameter Identification for Curli Fiber Expression Model*

| Kasielke, Stefanie | Zuse Insititute Berlin |
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In systems biology, one is often faced with the problem of incomplete data which usually leads to the existence of a large number of alternative models with indistinguishably good data fit. Traditional modelling approaches evertheless arrive at a single model. An alternative is to consider a set of models, all in agreement with the available data. We started with a pool of discrete models, given as a set of network topologies, and translated this pool into a single generic ODE model comprising all previously identified logical connections in terms of products or sums of Hill functions. In our setting the influence of each term on the species are defined by a specific factor, which acts as scaling and weighting. Our aim was to estimate the unknown parameter values in this model based on experimental measurement data. Ideally, we will arrive at parameter distributions or sets of possible

parametrizations that all match the time series data equally well. The main difference to other approaches, compare Schaber2012, Raue2015, Vaga2014 and Kuepfer2007, is that all possible models are summarized in one system of ordinary differential equations. The equations kept as simple as possible to get an indication for the most important pathways from quantitative data at once. So that there is no need to use quality measures as comparison between each considered model like Akaike information criterion, compare Schaber2012. To approximate the switch behaviour coming from the boolean models we focused on Hill kinetics and kept the number of parameters to calculate as small as possible. The parameters were estimated by using multistart local optimization in combination with simulated annealing. We finally analyzed the distributions in order to, e.g., quantify the importance of mechanisms or to find differences between cell lines. The weight of a logical connection was estimated by using the value of a factor relative to the sum of all factor values in the equation. To validate the methodology we used a model pool, consisting of ten different discrete models, for curli fiber expression in Escherichia coli examined concerning bistability by Yousef2015. The ten models were transformed into an ...

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| 12:10-14:10 | MoPP.24 |
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*Robustness and Filtering Properties of Ubiquitous Signaling Network Motifs*

| Paul, Debdas | Univ. of Stuttgart |
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| Radde, Nicole | Univ. of Stuttgart |

Biological systems are intrinsically robust. The system, being an open one, is permanently exposed to perturbations due to external noise from the surrounding environment. In this context, the architecture and information processing capabilities of a signaling network play an important role in attenuating the noise. Multi-layered phosphorylation cascades are architectures prevalent in some of our major signaling pathways. In this work, we investigate the robustness of such signaling cascades with respect to external input variations. We employ local sensitivity and output-variance based sensitivity as measures of robustness for such cascades and observe that the efficiency of high frequency signal attenuation increases with the number of in the cascades. Filtering properties of cascades have been observed previously but not under a very rigorous theoretical framework and not in comparison with other models. This work provides an example of optimality versus robustness tradeoff in the design principles of biological systems.

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| 12:10-14:10 | MoPP.25 |
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*Zero-Retroactivity Subtraction Module for Embedded Feedback Control of Chemical Reaction Networks*

| Bilotta, Mariaconcetta | Univ. Degli Studi Magna Graecia Di Catanzaro |
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| Cosentino, Carlo | Univ. Degli Studi Magna Graecia Di Catanzaro |
| Merola, Alessio | Univ. Degli Studi Magna Graecia Di Catanzaro |
| Bates, Declan G. | Univ. of Warwick |
| Amato, Francesco | Univ. Degli Studi Magna Graecia Di Catanzaro |

The control of biochemical processes is a major goal in systems and synthetic biology. Current approaches are based on ad-hoc designs, whereas a general and modular framework would be highly desirable, in order to exploit the well-assessed methods of control theory. A well-known problem when dealing with complex biosystems is represented by the retroactivity effect, which can significantly modify the dynamics of interconnected subsystem, with respect to the behaviour they exhibit when disconnected from each other. In the present work an implementation of a zero-retroactivity Chemical Reaction Network Subtractor (CRNS) is proposed and its effectiveness is investigated through singular perturbation analysis. The proposed CRNS represents a first step towards the development of a modular framework for the design of CRN-based embedded feedback control systems.

| 12:10-14:10 | MoPP.26 |
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*Irreversible Port-Hamiltonian Approach to Modeling and Analyzing of Non-Isothermal Chemical Reaction Networks*

| Wang, Li | Univ. of Groningen |
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| Maschke, Bernhard | Univ. De Lyon; Univ. Lyon 1, |
| van der Schaft, Arjan J. | Univ. of Groningen |

Inspired by great advances on the mathematical structure of chemical reaction networks governed by mass action kinetics and by one of the main features of Irreversible port-Hamiltonian formulation that the thermodynamic principles could be presented clearly and directly in its structure, the aim of our work is to utilize the Irreversible port-Hamiltonian formulation to study chemical reaction networks in non-isothermal case, including modeling, equilibrium and asymptotic stability.

| 12:10-14:10 | MoPP.27 |
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*Inferring the Effects of Positive and Negative Auto-Regulation under the Presence of Signalling Processes of Different Speed and Its Application to Inflammasome Signalling*

| Lopez-Caamal, Fernando | Univ. Nacional Autonoma De Mexico-UNAM |
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| Huber, Heinrich | Royal Coll. of Surgeons in Ireland |

Abstract: NLRP3-dependent inflammasome signaling is a key pathway during inflammatory processes. Its deregulation is implicated in several diseases such as congenital auto-immune-disorders, inflammatory bowel disease and myocardial infarction. The NLRP3-inflammasome pathway is invoked by a two-step receptor activation [1]. This activation leads to the rapid, phosphorylation-driven nfkB-pathway signaling. It subsequently proceeds via slower transcription/translation process for producing pro-enzymes, and finally leads to the medium-speed enzymatic activation of the central inflammatory mediator IL-1B. We here were interested how these different kinetics under the presence of a positive and negative auto-regulation would translate into a robust, stable and ultrasensitive IL-1B-activation. We therefore extracted the essential topology of the inflammasome pathway network using a linear chain of first order equations and a second order equation for inhibitory feedback. We then performed an analytical treatment of the resulting ODE system to obtain closed formulas. We therefore looked for stability and steady state conditions using a Jacobian-based local sensitivity analysis and employing the small gain theorem from control theory as recently applied by us [2]. We found that the presence of both feedbacks led to two steady states. The stability properties of these states were characterized exactly in terms of the kinetic parameters by closed formulas. We thereby were able to give a minimum reaction kinetics that is required to sustain robust IL-1B activation. While ablating the negative feedback only preserved the trivial steady state, ablating the positive feedback maintained both steady states, but rendered the non-trivial steady state as biologically unreasonable. In conclusion, our preliminary results suggest that in the core pathway of inflammasome signalling, the simultaneous presence of a positive and negative auto regulation is necessary to sustain stable IL-1B activation. We further propose that a minimum speed of protein production is essential to guarantee a stable inflammatory response, as otherwise inflammation would proceed transiently and in a volatile, non-regulated way.

| 12:10-14:10 | MoPP.28 |
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*Modulation of Noise in Regulatory Circuits for a Controlled Generation of Population Heterogeneity*

| Hahl, Sayuri Katharina | Tech. Univ. München |
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| Kremling, Andreas | Tech. Univ. München |

Heterogeneity within isogenic populations might constitute an evolutionary advantage. Therefore, some regulatory circuits enable the coexistence of multiple protein expression states under identical environmental conditions, thereby creating a variety of possible phenotypes. Transitions between states are promoted by intrinsic cellular noise, which results from the stochasticity of biochemical processes. In our study, we examine how an appropriate circuit design can precisely adjust transition probabilities by ensuring the desired noise level for each expression state. That way, population distributions can be controlled. In particular, bimodal activation patterns can be explained, where the low-expression state is subject to significant fluctuations so that a subpopulation of cells is randomly activated, whereas the high-expression state is robustly maintained due to efficient noise attenuation. The first part of our study deals with the choice of the modeling approach. Heterogeneity has often been attributed to deterministic bistability. However, significant differences between deterministic and stochastic model behavior can emerge in mesoscopic reaction systems: We show that nonlinear reaction propensities combined with large stoichiometric coefficients can lead to bistable but unimodal, and to monostable but bimodal systems. This is relevant in the context of gene expression where protein production might be subject to nonlinear activation or inhibition patterns and often occurs in bursts. For these reasons, we use the Chemical Master Equation to study noise in single-gene autoregulatory circuits. We identify topological and kinetic features that determine the variance of protein fluctuations as well as the occurrence of translational bursts - two important characteristics that have a combined effect on the robustness of cellular states. Based on this quantitative framework, we show that some circuit properties are suitable for regulating the overall noise characteristics in the system, while others can even modulate noise around each expression state of a multistable system separately. These findings give insight into possible control mechanisms of stochastic decision-making processes.

| 12:10-14:10 | MoPP.29 |
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*Stochastic Control with Poorly Known Biological Growth Models*

| Silva, Vinícius Lima | Univ. of Campinas |
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| Do Val, Joao B.R. | Unicamp - Feec |

Mathematical models used to represent growth patterns in biological applications offer a rough description of the corresponding biological processes, which induces uncertainties in problems involving growth models. We propose to study a general control problem of a system with dynamics described by two of these models under the Control Variation Increases the Uncertainties - CVIU - approach, aimed at controlling uncertain stochastic systems. Numerical results show the proposed approach performs better than the LQG controller in scenarios with large uncertainties.

| 12:10-14:10 | MoPP.30 |
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*Effective Detection of Multistationarity in Signaling Pathways with and without Mass Conservation*

| Otero-Muras, Irene | IIM-CSIC |
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| Yordanov, Pencho | ETH Zurich |
| Stelling, Joerg | ETH Zurich |

We develop an algorithm to efficiently search for mutistability sources in signaling pathways under specific biological/experimental conditions. The method exploits structural properties of biochemical networks derived from the Chemical Reaction Network Theory, and combines optimization and continuation techniques. Applying our method to the Interferon Signaling pathway, we detect bistability at the level of early STAT signaling, contributing to explain the differential signaling (antiviral vs antiproliferative) observed in type I IFNs.

| 12:10-14:10 | MoPP.31 |
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*Unravelling the Mechanisms of Bistability in Flagellar Gene Regulation*

| Koriala, Santosh | Univ. of Illinois |
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| Aldridge, Phillip | Newcastle Univ. |
| Rao, Christopher V. | Univ. of Illinois |

We investigated the mechanisms governing the bistable expression of the flagellar genes in *Salmonella enterica*. Using a

combination of mathematical modeling and experimental analysis, we demonstrate that the flagellar gene network encodes two bistable switches that operate in series. In the process, we have furthered our understanding of this complex gene network.

| 12:10-14:10 | MoPP.32 |
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*Iterative Multiple Linear Regression for Source Inversion in Graphs*

| Weber, Tobias | OvG Univ. Magdeburg |
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| Scholz, Eberhard | Univ. Hospital Heidelberg |
| Sager, Sebastian | OvG Univ. Magdeburg |

Ventricular tachycardia where a single source causes arrhythmic extra heart beats, i.e. frequent premature ventricular complexes, can be treated by catheter ablation of the source. The procedure consists of two parts: First the operator takes measurement on the inner surface of the heart heuristically until he finds the source. Then he ablates it. Modern sensoring allow to track the used catheter in 3D and make it possible to map the chamber geometry before taking measurements. This paper discusses an algorithm to support the search process on the inside of the heart chamber aiming at minimizing the number of necessary measurement points. The algorithm is implemented as a prototype in Matlab and tested in simulations based on real patient data. The performance of the algorithm is compared to the number of measurements taken in real treatments performed in the hospital.

| 12:10-14:10 | MoPP.33 |
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*The Impact of Experimental Data Quality on Computational Systems Biology and Engineering*

| Carius, Lisa | OvG Univ. Magdeburg |
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| Findeisen, Rolf | OvG Univ. Magdeburg |

The success of computational methods in systems biology and systems engineer- ing relies on the availability of mathematical models which represent the biological system adequately. The process of model development, model analysis and model invalidation is, however, often limited by the availability of suitable experimental data leading to impaired significances of the models. Especially mathematical models build for the purpose of process control, optimization and analysis have to represent and predict the behavior of the system very well. But how to generate experimental data which is suitable for computational systems biology and engineering? In this work we demonstrate that the close connected use of experimental and theoretical methods can be the key for deriving experimental data and mathematical models of a high quality. As a first step the experimental conditions which cause the desired systems behavior have to be identified and maintained. Poor process control strategies or a general lack of control engineering are often the bottleneck, impeding a systematic experimental approach. Here we show, by applying methods from bioengineering, systems biology and control engineering, how an experimental platform can be created which allows to address systems biological questions systematically. The shown approach stabilizes the process around a chosen working point so that the reaction of the system to a defined stimulation of an input can be monitored whilst the remaining process variables are kept constant. In that way dynamic system responses can be assigned to the change of a single input and hierarchical information of complex biological systems are revealed. In this work we use our approach to study the formation of photosynthetic membranes (PM) under microaerobic conditions in Rhodospirillum rubrum.

| MoPAP | Nave |
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| **Frank Doyle** (Plenary Session) | |
| Chair: Findeisen, Rolf | OvG Univ. Magdeburg |

| 14:10-15:00 | MoPAP.1 |
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*Systems Approaches to Treating Diabetes*

| Doyle, Francis | Harvard Univ |
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Diabetes is a disease that afflicts over 400 million individuals

worldwide and is characterized by a dysregulation of blood sugar levels in the blood. In type 1 diabetes, the beta cells in the pancreas are destroyed, removing endogenous insulin production and thus necessitating exogenous insulin administration. In type 2 diabetes, the more prevalent version, insulin is produced,but the body fails to respond appropriately. Over the years our group has studied both type 1 and type 2 diabetes, with model-based control systems approaches for the optimal delivery of insulin, and robust control approaches to the identification of drug targets in the cellular regulatory network. I will provide an overview of the systems biology approaches employed by our group to study diabetes, from signaling models to pharmacokinetic/pharmacodynamic patient models. These methods enable the personalized and predictive medicine approaches that are receiving increasing attention. The role of models and control theoretic sensitivity analyses in both drug targeting and drug delivery will be detailed. A novel application of the structured singular value to the glucose signaling network will be shown, with relevance to type 2 diabetes drug targets. Finally, encouraging clinical results from over 1000 individual patient tests will be described, including systems issues for FDA review as well as a path to eventual commercialization.

| MoKAP | Nave |
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| **Rudi Gunawan** (Keynote Session) | |
| Chair: Picó, Jesús | Univ. Pol. De Valencia |

| 15:10-15:40 | MoKAP.1 |
|---|---|

*Gene Regulatory Network Inference Using Time-Stamped Cross-Sectional Single Cell Expression Data*

| Papili Gao, Nan | ETH Zurich |
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| Ud-Dean, S. M. Minhaz | ETH Zurich |
| Gunawan, Rudiyanto | ETH Zurich |

In this paper we presented a novel method for inferring gene regulatory network (GRN) from time-stamped cross-sectional single cell data. Our strategy, called SNIFS (Sparse Network Inference For Single cell data) seeks to recover the causal relationships among genes by analyzing the evolution of the distribution of gene expression levels over time, more specifically using Kolmogorov-Smirnov (KS) distance. In the proposed method, we formulated the GRN inference as a linear regression problem, where we used Lasso regularization to obtain the optimal sparse solution. We tested SNIFS using in silico single cell data from 10- and 20-gene GRNs, and compared the performance of our method with Time Series Network Inference (TSNI), GEne Network Inference with Ensemble of trees (GENIE3), and an extension of GENIE3 for time series data called JUMP3. The results showed that SNIFS outperformed existing algorithms based on the Area Under the Receiver Operating Characteristic (AUROC) and Area Under the Precision-Recall (AUPR) curves.

| MoA1 | Nave |
|---|---|
| **Modelling – Microbial Systems** (Regular Session) | |
| Chair: Westerhoff, Hans | Univ. of Manchester and Amsterdam |
| Co-Chair: Bernaerts, Kristel | Univ. of Leuven (KU Leuven) |

| 16:10-16:30 | MoA1.1 |
|---|---|

*In Silico Analysis of Clostridium Difficile Biofilm Metabolism and Treatment*

| Henson, Michael A. | Univ. of Massachusetts |
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| Phalak, Poonam | Univ. of Massachusetts |

*Clostridium difficile* is an anaerobic bacterium responsible for recurring infections in the gastrointestinal tracts of patients previously treated with oral antibiotics that disrupt the healthy gut microbiome. Recent in vitro experiments have demonstrated the ability of *C. difficile* to form biofilms on surfaces. We developed a metabolic model of *C. difficile* biofilms to investigate the effects of

biofilm formation on antibiotic treatment in vivo. The model was formulated by combining a genome-scale reconstruction of *C. difficile* primary metabolism with reaction-diffusion type equations for key nutrients (glucose and six essential amino acids) and the common oral antibiotic vancomycin. A very simple model of vancomycin pharmacokinetics was used to predict the efficacy of a typical treatment schedule under the assumption of a fixed thickness of the mature biofilm. Our model predicted that vancomycin will effectively eradicate biofilms of sufficiently small thickness. Once the thickness passed a critical threshold, the model predicted vancomycin treatment would fail catastrophically due to insufficient antibiotic penetration into the biofilm caused by the combination of limited diffusion and vancomycin binding to cell wall precursors. This critical biofilm thickness was shown to be very sensitive to model parameters associated with the vancomycin stool levels and killing efficiency.

| 16:30-16:50 | MoA1.2 |
|---|---|

*Dynamic Macroscopic Model of Dengue Viral Amplification in Vero Cell Cultures*

| Abbate, Thomas | Univ. De Mons |
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| Dewasme, Laurent | Univ. De Mons |
| Vande Wouwer, Alain | Univ. De Mons |

In this work, a dynamic model of infection and virus amplification in vero cell cultures targeting vaccine production is proposed. In contrast with previous works, the model describes the process dynamics as functions of the whole living (uninfected and infected) biomass. The dynamic model is based on a slow-fast approximation where the infected biomass is considered as evolving faster than other variables. The resulting model contains unknown parameters that are inferred from datasets collected from an actual vaccine production process. Parameter identification is complemented by a sensitivity analysis and the determination of confidence intervals for the parameters and predicted trajectories. Results are in general in good agreement with the experimental data.

| 16:50-17:10 | MoA1.3 |
|---|---|

*Protein-Level Control of Metabolism: Design Principles and Prospects from a Representative System*

| Euler, Christian K. | Univ. of Toronto |
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| Mahadevan, Radhakrishnan | Univ. of Toronto |

Significant evidence suggests protein-level or metabolic control is widespread and important in metabolic networks. However, the biophysical interactions responsible for flux control at the metabolic level are not nearly as well-characterized as those which are responsible for control at other biological levels, such as transcriptional regulation. This knowledge gap is a limiting factor in the application of engineered protein-level regulation in Metabolic Engineering for the rational and sensitive control of pathway flux. Here we apply an in silico dynamic numerical optimization approach to a representative branched pathway to understand how engineered allosteric regulation could be used to control flux. We consider inhibition sensitivity as a hypothetical tuneable parameter to demonstrate that integration of allosteric and transcriptional regulation is necessary to stably achieve arbitrary targets for both downstream metabolite concentrations. We further show that the steady-state ratio of these metabolites can be controlled by tuning the sensitivity of allostery at the branch point. Finally, we demonstrate that system dynamics dictate which type of engineered control is optimal. This work has implications for the co-optimization of transcriptional and allosteric regulatory systems in metabolic networks and provides a framework for the design of allosteric regulation in engineered metabolisms.

| 17:10-17:30 | MoA1.4 |
|---|---|

*A Fokker-Planck Equation Formalism to Model Bacterial Growth and Cell Size*

| García, Míriam R. | IIM-CSIC |
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| Alonso, Antonio A. | IIM-CSIC |
| Teixeira, Isabel | IIM-CSIC |

| Vázquez, José Antonio | Grupo De Reciclado Y Valorización De Materiales Res. |
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Understanding cell-to-cell variability is fundamental to quantitatively assess the risk of food-borne outbreaks. The main challenge is to find a fast and reliable model that takes into account this variability and simultaneously addresses small and large populations. Individual-based modelling is the usual choice when heterogeneity has to be considered. However, computations tend to be prohibitive for simulations above certain number of individuals. In addition, numerical estimation of the probability density function is a challenge problem where usually certain type of distribution has to be assumed.

In this work we derived a modified Fokker-Plank equation to predict cell size and division. The model describes the population growth and the evolution of the cell sizes during the exponential phase. We also provide evidence of the model capability to explain growth and cell size of Pediococcus acidilactici measured using flow cytometry.

| 17:30-17:50 | MoA1.5 |
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*A Collection of Mathematical Models Showing Diauxic Growth Behaviour*

| Kremling, Andreas | Tech. Univ. Munich |
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The modelling of cellular systems is still a challenging task. Taking the example of carbon catabolite repression a number of models are described and discussed in literature. Using a simple model structure where two substrates are taken up by biomass we provide a collection of around 20 models all showing diauxic growth behavior. The models differ only in a single aspect that is sufficient to break the symmetry of substrate uptake. By comparing simulation results with experimental data for growth on glucose and lactose, a number of models already can be excluded from the list of possible mechanisms in this case.

| MoA2 | Gallery |
|---|---|
| **Methods** (Regular Session) | |
| Chair: Stelling, Joerg | ETH Zurich |
| Co-Chair: Balsa-Canto, Eva | CSIC |

| 16:10-16:30 | MoA2.1 |
|---|---|

*Structural Identifiability Analysis Via Extended Observability and Decomposition*

| Fernández Villaverde, Alejandro | Univ. De Vigo |
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| Barreiro, Antonio | Univ. of Vigo |
| Papachristodoulou, Antonis | Univ. of Oxford |

Structural identifiability analysis of nonlinear dynamic models requires symbolic manipulations, whose computational cost rises very fast with problem size. This hampers the application of these techniques to the large models which are increasingly common in systems biology. Here we present a method to assess parametric identifiability based on the framework of nonlinear observability. Essentially, our method considers model parameters as particular cases of state variables with zero dynamics, and evaluates structural identifiability by calculating the rank of a generalized observability-identifiability matrix. If a model is unidentifiable as a whole, the method determines the identifiability of its individual parameters. For models whose size or complexity prevents the direct application of this procedure, an optimization approach is used to decompose them into tractable subsystems. We demonstrate the feasibility of this approach by applying it to three well-known case studies.

| 16:30-16:50 | MoA2.2 |
|---|---|

*Identification of Functional Connections in Biological Neural Networks Using Dynamical Bayesian Networks*

| Dong, Chaoyi | Inner Mongolia Univ. of Tech |
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| Yue, Hong | Univ. of Strathclyde |

Investigation of the underlying structural characteristics and network properties of biological networks is crucial to understanding the system-level regulatory mechanism of network behaviors. A Dynamic Bayesian Network (DBN) identification method is developed based on the Minimum Description Length (MDL) to identify and locate functional connections among Pulsed Neural Networks (PNN), which are typical in synthetic biological networks. A score of MDL is evaluated for each candidate network structure which includes two factors: i) the complexity of the network; and ii) the likelihood of the network structure based on network dynamic response data. These two factors are combined together to determine the network structure. The DBN is then used to analyze the time-series data from the PNNs, thereby discerning causal connections which collectively show the network structures. Numerical studies on PNN with different number of nodes illustrate the effectiveness of the proposed strategy in network structure identification.

| 16:50-17:10 | MoA2.3 |
|---|---|

*Reconstruction of Ensemble of Single-Cell Time Trajectories from Discrete-Time Fluorescence Data: Oscillatory MAPK Dynamics*

| Kalantre, Girija S. | Indian Inst. of Tech. Bombay |
| Viswanathan, Ganesh A. | Indian Inst. of Tech. Bombay |

Continuous time profiles of intracellular protein levels in a collection of isogenic cells is needed to achieve quantitative prediction of heterogeneity in cellular systems. However, intracellular staining based quantitative single-cell detection of protein levels, reported by emitted fluorescence, using confocal microscopy or flow cytometry can only result in discrete time series due to arresting of cell state to enable entry of reporters – antibody – into the cell. We propose a method to reconstruct the time-series of oscillatory dynamics of phosphorylated ERK (pERK), the terminal protein in the ubiquitously found MAPK cascades, based on the discrete time series data consisting of a distribution of fluorescence emitted by different ensemble of cells at different time points post-stimulation. This method employs a model autocorrelation function to predict the fluorescence from the experimental data that will correspond to a specific time point in a randomly reconstructed trajectory. We validate the method using the single-cell pERK oscillatory dynamics data consisting of 12100 data points measured in transfected cells across 121 time points by pairing reconstructed trajectories with those from original based on the constraint that the pair satisfied a certain cut-off for both mutual information score and Euclidean distance between them. Out of the 100 trajectories in the original data, our algorithm was able to reconstruct ~30 of them capturing a reasonable fraction of the amplitudes of the Fast fourier transform modes present in the original trajectory. Using the developed method, we reconstructed 2471 trajectories from pERK discrete dynamics data set consisting of distribution of fluorescence data across 16 time points obtained from single-cell flow cytometry. The dynamics of the standard deviation of the reconstructed trajectories is comparable to that of the original fluorescence data.

| 17:10-17:30 | MoA2.4 |
|---|---|

*Analysis of Circadian Cellular Bioluminescence Recordings Using a Kalman Smoother*

| Ananthasubramaniam, Bharath | Charite Univ |

Circadian clocks permit mammals to adapt to their periodic natural environment. These clocks generate rhythms in the expression of genes and proteins in most tissues within the organism. Real-time bioluminescence recordings of gene or protein expression in an important tool to study the clock under different manipulations and conditions. Here, we present a tool to extract useful characteristics of the cellular rhythms, such as period and damping rate, using maximum-likelihood estimation in a stochastic damped oscillator model. The tool uses the expectation-maximization algorithm in combination with a Kalman Smoother to perform the joint state and parameter estimation. We apply this tool to quantify the differences between rhythms in the master circadian clock in the brains of two different knockout mice and compare the results to a standard autocovariance fitting-based approach for parameter estimation.

| 17:30-17:50 | MoA2.5 |
|---|---|

*Efficient Computation of All Distinct Realization Structures of Kinetic Systems*

| Tuza, Zoltan A. | Univ. of Stuttgart |
| Acs, Bernadett | Pazmany Peter Catholic Univ |
| Szederkenyi, Gabor | Comp. and Aut. Inst. Hungarian |
| Allgöwer, Frank | Univ. of Stuttgart |

Structural non-uniqueness of (bio)chemical reaction networks realizing a given kinetic dynamics has been known for a long time, but it is often overlooked in practice. However, without appropriate prior information, this phenomenon seriously hinders the successful identification of biochemical models. Recently, an algorithm with guaranteed polynomial time complexity between iterations has been developed to compute all distinct reaction graph structures corresponding to a given dynamics. This paper presents an improved version of this algorithm that is suitable to take the advantage of a multiprocessor environment. The computed structures are collected in a task queue, and two server processes coordinate the operation of the set of workers. The implementation is briefly described and the performance of the approach is illustrated on computational examples taken from the literature.

# Program and Abstracts Tuesday October 11

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|---|---|
| 08:30-09:15 TuPMP, Nave, **Plenary Hans Westerhoff** | |
| 09:15-09:45 TuKMP, Nave, **Keynote Bas Teusink** | |
| 7 | |
| 10:20-12:00 TuM1, Nave<br>**Dynamics and Control** | 10:20-12:00 TuM2, Gallery<br>**Optimization Based Methods for Understanding the Regulation of Cellular Metabolism** |
| 12:00-14:00 TuPP,  TM, **Poster Session II with Lunch** | |
| 14:00-14:30 TuKA1P, Nave, **Keynote Pablo Iglesias** | |
| 14:30-15:00 TuKA2P, Nave, **Keynote Jörg Stelling** | |
| 15:00-15:20 TuCAP,  Nave, **Coffee Break** | |
| 15:20-17:00 TuA1, Nave<br>**Session in Memoriam of Peter Wellstead** | 15:20-17:00 TuA2, Gallery<br>**Biotechnology Methods & Applications** |
| 17:30-23:00 TuRP, **Conference Banquet and Boat Tour** | |

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**TuPMP** Nave

**Hans Westerhoff** (Plenary Session)

| Chair: Bernaerts, Kristel | Univ. of Leuven (KU Leuven) |
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08:30-09:15 TuPMP.1

*Maps for When the Living Gets Tough: Maneuvering through a Hostile Energy Landscape*

| Mondeel, Thierry D.G.A. | Univ. of Amsterdam |
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| Rehman, Samrina | Univ. of Manchester |
| Zhang, Yanfei | Univ. of Amsterdam |
| Verma, Malkhey | Central Univ. of Punjab |
| Dürre, Peter | VU Univ. Amsterdam |
| Barberis, Matteo | Univ. of Amsterdam |
| Westerhoff, Hans V. | Univ. of Amsterdam, Univ. of Manchester, VU Univ. |

With genome sequencing of thousands of organisms, a scaffold has become available for data integration: molecular information can now be organized by attaching it to the genes and their gene-expression products. But of course, it is the genome that is selfish not the gene. By using mass conservation and balance relationships, the metabolic part of the functioning genome can be organized into a maps that enable functional interpretation of the fitness of the genome, and hence of its genes collectively. Using flux balance analysis one can liven up such genome-wide metabolic maps and calculate the theoretical capabilities of the living organism. Here we shall discuss how this elucidates how organisms such as the ones present when life on earth began, are able to assimilate the Gibbs energy and Carbon that Life needs for its reproduction and maintenance, from their Gibbs-energy-poor environment. We shall address how C. ljungdahlii may use at least two special features and one special pathway to this end, i.e. gear-shifting, electron bifurcation and the Wood-Ljungdahl pathway. The gear-shifting is needed because of the fairly high Gibbs energy quant in ATP. We will discuss a similar network-based gear shifting in S. solfataricus. Since the Wood-Ljungdahl pathway uses hydrogen gas and has CO as an intermediate, we examined whether the C. ljungdahlii map can also help solve a less academic problem, i.e. the management of waste. We find that the organism itself might be able to turn hydrogen gas and CO, which as syngas becomes available upon incineration of waste, into biodegradable plastic, provided it is engineered with two additional genes.

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**TuKMP** Nave

**Bas Teusink** (Keynote Session)

| Chair: Waldherr, Steffen | KU Leuven |
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09:15-09:45 TuKMP.1

*Regulation of Metabolism: Navigating between Desired and Fatal States*

| Teusink, Bas | VU Univ. Amsterdam |
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Cells evolved a remarkable ability to adapt to environmental conditions, or to withstand otherwise detrimental mutations. These properties arise from the integrative functioning of biological networks. Functional genomics has allowed the cost-effective measurement of the network components; however, we still mostly fail to understand how their interactions lead to cellular function and adaptation. One view that is becoming dominant in cellular physiology, is that physical and (bio)chemical constraints limits protein content and synthesis, impacting how resources are partitioned over growth and stress processes to optimize fitness ("cellular economics"). This view contrasts current mainstream modeling efforts at the genome-scale, which are largely focussed on the metabolic network only, and subsequently they often fail to predict the proper regulation of fluxes. I will show with some practical examples, however, when and how these models are still useful, and how we can integrate the cellular economy into these models. Still, the resource allocation perspective is developed for steady-state growth under constant environments, and mostly for E. coli. Whether this perspective is relevant for other microorganisms remains unclear. Moreover, what happens during transitions between steady-state growth conditions is largely unexplored. Recent studies in yeast show that the response time after a nutrient change is an evolvable trait that is dependent on nutrient dynamics and comes at the cost of balanced growth rate. We showed that an intricate and dynamic regulatory mechanism is in place in yeast to ensure robustness during glucose transitions. Thus, the aim of this talk is to illustrate how regulation of metabolism is an intruiging balancing act between desired and fatal states, shaped by constraints and trade-offs.

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**TuM1** Nave

**Dynamics and Control** (Regular Session)

| Chair: Iglesias, Pablo A. | Johns Hopkins Univ |
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| Co-Chair: Jayawardhana, Bayu | Univ. of Groningen |

10:20-10:40 TuM1.1

*Control of the Production of Saccharomyces Cerevisiae on the Basis of a Reduced Metabolic Model*

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| Wegerhoff, Sven | TU Dortmund |
| Engell, Sebastian | TU Dortmund |

*Saccharomyces cerevisiae* is a species of yeast with a long tradition in human history and a growing demand in industry and research. The yeast cells itself are produced in a series of fed batch reactors which are fed by oxygen and glucose as the main carbon source. One problem during the production process is that the cell culture can switch to undesired ethanol production leading to a lost batch. For improving the production process a suitable modeling and control strategy is needed that should cover the switch to ethanol production and should be able to describe the growth of the cell culture to enable an optimal yield. This work presents a novel method that uses dynamic flux balance analysis to derive a reduced metabolic model from a full biochemical stoichiometric network which is then used for setting up a model predictive control. The reduced metabolic model covers the gene regulation by using the redox metabolites as key regulators. It is shown that this modeling approach is very flexible and can be used to control and to monitor the process.

| 10:40-11:00 | TuM1.2 |
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*Bistability and Non-Monotonic Induction of the Lac Operon with Lactose*

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| Zander, Dominique | Max-Planck-Inst. for Dynamics of Complex Tech. Systems |
| Straube, Ronny | Max-Planck-Inst. for Dynamics of Complex Tech. Systems |
| Bettenbrock, Katja | Max Planck Inst. for Dynamics of Complex Tech. Systems |

The E. coli lac operon is paradigm of genetic regulation. Although bistability of lac operon expression has been shown for gratuitous inducers, bistability is actively debated for induction with the natural substrate lactose. Analysis of lac operon induction with lactose was performed both experimentally as well as by modelling studies. The results show a graded and non-monotonic induction with increasing lactose concentrations. lac operon expression is not bistable in the wildtype but can be driven to bistability by overexpression of lactose repressor.

| 11:00-11:20 | TuM1.3 |
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*Optimal Scheduling of Vaccination Campaigns Using a Direct Dynamic Optimization Method*

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| Correa Cordova, Max Leo | Tech. Univ. Ilmenau |
| Geletu, Abebe | Tech. Univ. Ilmenau |
| Li, Pu | Tech. Univ. Ilmenau |

The scheduling of vaccination campaigns determines the feasibility and effectiveness of controlling the proliferation of an epidemic disease. Optimal vaccination strategies can be derived by using optimization methods. However, most of the solution approaches for this target have been based on the indirect dynamic optimization methods, leading to limitations in the scheduling of vaccination campaigns. In this study, the scheduling problem is solved by an efficient direct method known as the combined shooting and collocation approach. In this way, both control and state constraints can be efficiently treated. More importantly, this method allows solving the problem with multiple impulsive vaccinations at arbitrary time points. As a result, the quality of the vaccination can be essentially improved in comparison to the results from the literature.

| 11:20-11:40 | TuM1.4 |
|---|---|

*Contractivity of a Genetic Circuit with Internal Feedback and Cell-To-Cell Communication*

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| Picó-Marco, Enric | Univ. Pol. De Valencia |
| Boada, Yadira | Univ. Pol. De València |
| Picó, Jesús | Univ. Pol. De Valencia |
| Vignoni, Alejandro | Max Planck Inst. of Molecular |

Cell Biology and Genetics

We consider a realistic model of the synthetic gene circuit combining cell-to-cell communication system via quorum sensing, and a synthetic repressible promoter implementing intracellular negative feedback control. The circuit has been shown to increase robustness with respect to both extrinsic and intrinsic noise elsewhere. As a first step towards an analytic analysis, in this paper we use contraction theory to perform a stability analysis. From it, we infer the components of the circuit most affecting the rate of contractivity, using biologically sensible values of the circuit parameters.

| 11:40-12:00 | TuM1.5 |
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*Model Reduction of Detailed-Balanced Reaction Networks by Clustering Linkage Classes*

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| Rao, Shodhan | Ghent Univ. Global Campus |
| Jayawardhana, Bayu | Univ. of Groningen |
| van der Schaft, Arjan J. | Univ. of Groningen |

We propose a model reduction method that involves sequential application of clustering of linkage classes and Kron reduction. This approach is specifically useful for chemical reaction networks with each linkage class having less number of reactions. In case of detailed balanced chemical reaction networks that are governed by general enzyme kinetics, we show that our procedure ensures that the space of equilibria corresponding to the original model is a subspace of the space of equilibria of the reduced model.

| **TuM2** | Gallery |
|---|---|
| **Optimization Based Methods for Understanding the Regulation of Cellular Metabolism** (Invited Session) | |
| Chair: Waldherr, Steffen | KU Leuven |
| Co-Chair: Bockmayr, Alexander | FU Berlin |
| Organizer: Waldherr, Steffen | KU Leuven |
| Organizer: Bockmayr, Alexander | FU Berlin |
| Organizer: Bruggeman, Frank | VU Amsterdam |
| Organizer: Hatzimanikatis, Vassily | EPFL |

| 10:20-10:40 | TuM2.1 |
|---|---|

*Can Bacteria Maximise Their Growth Rate, and If So, How? (I)*

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| Planque, Bob | Vrije Univ. Amsterdam |
| Hulshof, Josephus | Department of Mathematics, Vrije Univ. Amsterdam |
| Teusink, Bas | VU Univ. Amsterdam |
| Bruggeman, Frank | VU Amsterdam |

Microbes need to resist adverse conditions, grow when conditions are favourable. To outcompete their neighbours, fast growth and subsequent duplication is of prime importance. Bacteria attain high growth rates only when they use available resources economically. Perhaps paradoxically, the abundant biochemical detail underlying cellular physiology does not give quantitative insight into microbial growth rates. In this talk, we will present a simple but general framework that relates growth rates of balanced growth cultures to metabolic reaction rates. It is based on the observation that cellular growth is driven by osmotic pressure: the continuous build up of new macromolecules in the cell at fixed volume would cause osmotic pressure to build. The cell responds by enlarging its volume. By introducing a relation between cellular contents (copy numbers of different kinds of molecules and their molar volumes) and cellular volume, we derive a simple yet powerful formula for the growth rate in terms of metabolic rates. With this formula, we then show that calculating the balanced growth rate for a cell requires more than just stoichiometry, contrary to many current FBA approaches: rate laws governing individual reaction rates are

vitally important as well. Moreover, we prove for a general class of models that achieving maximal growth rate in given environmental conditions is realised in special minimal subnetworks, which we will call Elementary Growth Modes (EGMs). EGMs are akin to the better-known Elementary Flux Modes (EFMs), which also appear in optimisation problems for cellular metabolism. However, there are some important differences. Whilst EFMs always have one additional reaction to the number of metabolites, EGMs have equal numbers of each. More importantly, EGMs can not be computed on the basis of stoichiometry alone, but require reaction kinetics. Our work gives a new understanding of bacterial growth rate in terms of metabolic activity, and provides insight how growth rate may be maximised under varying conditions. This submission is part of the invited session ``Optimization based methods for understanding the regulation of cellular metabolism&apos;&apos;.

| 10:40-11:00 | TuM2.2 |
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*EColiCore2: A Reference Network Model of the Central Metabolism of Escherichia Coli and Relationships to Its Genome-Scale Parent Model (I)*

| Hädicke, Oliver | Max-Planck-Inst. for Dynamics of Complex Tech. Systems |
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| Erdrich, Philipp | Max-Planck-Inst. for Dynamics of Complex Tech. Systems |
| Klamt, Steffen | Max Planck Inst. for Dynamics of Complex Tech. Systems |

Genome-scale metabolic modeling has become an invaluable tool to analyze properties and capabilities of metabolic networks and has been particularly successful for the model organism Escherichia coli. The most recent genome-scale reconstruction iJO1366 is widely accepted as the reference E. coli network. However, for several applications, smaller metabolic (core) models are needed. Using ECGS, a slightly modified version of iJO1366, as parent model and the recently introduced NetworkReducer, we derived a subnetwork, EColiCore2 (ECC2) that preserves predefined phenotypes including optimal growth on different substrates. A systematic comparison of EColiCore2 with its genome-scale parent model iJO1366 reveals that several key properties (flux ranges, reaction essentialities, production envelopes) of the central metabolism are preserved in EColiCore2 while it neglects redundancies along biosynthetic routes. We also studied the value of the core model for calculating relevant metabolic engineering strategies by means of a case study with ethanol as product of interest. The reduced network EColiCore2 comprises 486 metabolites and 499 reactions, is accessible for elementary-modes analysis and can, if required, be further compressed to a network ECC2comp with 82 reactions and 54 metabolites having an identical solution space as ECC2. All flux distributions in ECC2 are valid solutions in ECGS and, likewise, all elementary modes of ECC2 are equally valid in ECGS. Reaction knockout sets of ECC2 can be used as a seed and then be extended by further knockouts to a valid strategy for ECGS. We demonstrated that this approach can be used to determine thousands of additional valid knockout strategies for ECGS with higher cardinalities which could not be calculated before. A major advantage of ECC2 is that it is a strict submodel of its genome-scale parent model ECGS by which results from ECC2 can be directly related to ECGS. ECC2 allows for the full enumeration of elementary modes and metabolic engineering strategies and it is readily usable for educational purposes due to its appropriate scope, size, and clarity. Overall, EColiCore2 holds promise to become a reference model of E. coli&apos;s central metabolism.

| 11:00-11:20 | TuM2.3 |
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*Theoretical Aspects of Bacterial Growth (I)*

| Klumpp, Stefan | Univ. of Göttingen/MPI Potsdam |
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Genetic circuits perform logical operations similar to electric circuits. However, genetic circuits are never fully decoupled from the background processes going on in the cell, because the molecular machinery processing the genetic information is shared with all other genes. Exponential growth of bacteria can be used as a model system to study this coupling. The talk will discuss

several aspects of bacterial growth from a modeling perspective including the effects of growth rate and the division cycle on gene circuits and the role of these effects in tolerance of bacterial populations to antibiotics.

This submission is part of the invited session „Optimization based methods for understanding the regulation of cellular metabolism".

| 11:20-11:40 | TuM2.4 |
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*Quantitative Prediction of Genome-Wide Resource Allocation in Bacteria (I)*

| Goelzer, Anne | INRA |
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| Fromion, Vincent | INRA |

Predicting resource allocation between cell processes is the primary step towards decoding the evolutionary constraints governing bacterial growth under various conditions1. Quantitative prediction at genome-scale remains a computational challenge as current methods are limited by the tractability of the underlying problem2 or by simplifying hypotheses. In this talk, we present the constraint-based modeling method Resource Balance Analysis (RBA). By considering the bacterial cell as a self-replicating system, the RBA method intrinsically captures the bottleneck due to resource sharing between all biological processes as a non-smooth convex feasibility problem that is efficiently solved through the resolution of an equivalent Linear Programming (LP) optimization problem. The optimal cellular configuration can be computed under the objective of growth rate maximization by solving a sequence of LPs. The refinement of the underlying mathematical description of cell processes compared to well-established constraint-based methods like Flux Balance Analysis5 entails inevitably an increased number of parameters in the model. By combining physiological and large-scale datasets (growth rate, fluxome, and absolute protein abundances), we succesfully calibrated RBA for the Gram-positive model bacterium Bacillus subtilis and showed that RBA accurately predicts the resource allocation for a wide range of growth conditions (Goelzer et al. Metab. Eng 2015). During the calibration process, the apparent catalytic rates of active metabolic enzymes are estimated and most of them are linearly decreasing with decreasing growth rate. The regulation of most cellular processes is consistent with the objective of growth rate maximization except for a few suboptimal processes which likely integrate more complex objectives such as coping with stressful conditions and survival. We also illustrate how calibrated RBA enables the prediction of complex strategies like managing the uptake of nutrients (carbon and/or amino acid sources) in complex medium. Altogether, RBA offers new opportunities to investigate design principles in prokaryotes and to exploit them for future biotechnological applications.

| 11:40-12:00 | TuM2.5 |
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*Evaluating the Stoichiometric and Energetic Constraints of Cyanobacterial Diurnal Growth (I)*

| Reimers, Alexandra-M. | Freie Univ. Berlin |
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| Knoop, Henning | Humboldt-Univ. Berlin |
| Bockmayr, Alexander | FU Berlin |
| Steuer, Ralf | Humboldt-Univ. Berlin |

Growth and proliferation entail a very well coordinated distribution of cellular resources to various intracellular processes, including the de-novo synthesis of proteins, lipids, as well as other cellular components.

For cyanobacteria, growth-dependent resource allocation is further subject to diurnal light-dark cycles that partition metabolism and growth into distinct phases and preclude a straightforward stationary analysis. Cyanobacteria are known to posses an endogenous circadian clock that has been shown to control metabolite partitioning during diurnal growth, and several experimental results show the relevance of time-specific synthesis of cellular components for cyanobacterial growth. Nonetheless the implications of a diurnal environment on the cellular resource allocation problem are insufficiently understood. Current computational approaches focus almost exclusively on heterotrophic growth at steady state and are hence not suitable to

study cyanobacterial phototrophic growth.

Here we present a comprehensive computational approach to evaluate the optimality of dynamic diurnal resource allocation in cyanobacteria. The focus is on the energetic constraints that shape the cellular "protein economy", i.e., the relationship between the average growth rate and the relative partitioning of metabolic, photosynthetic, and ribosomal proteins during a full diurnal period.

We demonstrate that, based on very few assumptions, one can derive quantitative predictions for questions like how is glycogen storage organized. Moreover, using our model we are able to predict reaction rate changes at genome scale, over the diurnal cycle, as well as the impact of growth rate on the relative amount of important cellular components such as the ribosome or the photosystems.

Our model provides a framework for the study of metabolic resource allocation at genome scale in the context of a day-night cycle.

| **TuPP** | free |
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| **Lunch + Poster Session II** (Poster Session) | |

| 12:00-14:00 | TuPP.1 |
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*Analyzing the Impact of Heterogeneity in Genetically Engineered Cell Lines for Influenza Vaccine Production Using Population Balance Modeling*

| Dürr, Robert | OvG Univ. Magdeburg |
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| Duvigneau, Stefanie | OvG Univ. Magdeburg |
| Laske, Tanja | OvG Univ. Magdeburg |
| Bachmann, Mandy | Max Planck Inst. for Dynamics of Complex Tech. Systems |
| Kienle, Achim | OvG Univ. Magdeburg |

Engineering of novel cell lines for biotechnological processes, e.g. influenza virus vaccine production, can be achieved by the genetic modification of host cell gene expression. Therefore, versatile genome editing methods such as lentiviral transduction can be applied to improve the production process. However, due to random integration of lentiviral-delivered genes in the host cell genome, nonuniform, i.e. heterogeneous, gene expression within the host cell population is expected. Within this contribution we investigate the influence of this cell-to-cell variability on important process variables like the maximum virus yield. Therefore, a multi dimensional population balance model is proposed which, on the one hand comprises a detailed description of the intracellular viral replication cycle and, on the other, also accounts for the expected heterogeneity in the host cell population. The results indicate that the overall vaccine production process can be improved by enhancement or inhibition of certain steps in the viral replication cycle. Furthermore, the achieved improvements show robustness against moderate degrees of cell-to-cell variability from genetic modification of host cells via transduction.

| 12:00-14:00 | TuPP.2 |
| --- | --- |

*Mathematical Modelling of Anaerobic Digestion with Hydrogen and Methane Production*

| Borisov, Milen | Inst. Mathematics and Informatics, Bulgarian Acad. of Sciences |
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| Dimitrova, Neli | Inst. Mathematics and Informatics, Bulgarian Acad. of Sciences |
| Simeonov, Ivan | Inst. of Microbiology, Bulgarian Acad. of Sciences |

We propose a new mathematical model describing a biotechnological process of simultaneous production of hydrogen and methane by anaerobic digestion. The process is carried out in two connected continuously stirred bioreactors. The proposed model is developed by reducing the well known Anaerobic Digester Model No 1 (ADM1). The mathematical analysis of the

model involves computation of equilibrium points, investigation of their local stability with respect to practically important input parameters, existence of maxima of the input-output static characteristics. Numerical simulations using a specially elaborated web-based software environment are presented to demonstrate the dynamic behavior of the model solutions.

| 12:00-14:00 | TuPP.3 |
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*Fusion Detection in Time-Lapse Microscopy Images: Application to Lipid Droplets Coalescence in Plant Seeds*

| Deslandes, François | MaIAGE, INRA, Univ. Paris-Saclay |
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| Laroche, Béatrice | MaIAGE, INRA, Univ. Paris-Saclay |
| Trubuil, Alain | MaIAGE, INRA, Univ. Paris-Saclay |

Detecting fusion events between lipid droplets of Arabidopsis thaliana embryos is of significant interest to understand the role of lipid droplet proteins. Lipid droplet proteins, called oleosins, have been shown to influence the size of lipid droplets possibly by preventing coalescence. We propose to detect fusion events in timelapse microscopy images of several oleosin deficient A. thaliana embryos. To detect volume preserving fusion events in a dense environment, we propose a procedure based on particle tracking and statistical tests. Using synthetic data, we compare the performances of our method to heuristic decision rules adapted from tracking algorithms from the literature.

| 12:00-14:00 | TuPP.4 |
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*Improving Bioprocess Productivity Using Constraint-Based Models in a Dynamic Optimization Scheme*

| Jabarivelisdeh, Banafsheh | OvG Univ. Magdeburg |
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| Waldherr, Steffen | KU Leuven |

Modulating the expression of target genes is an effective metabolic engineering approach to increase bioprocess productivity. In this work, a bilevel optimization framework is applied for dynamic manipulation of gene expression based on constraint-based models. A dynamic model in the inner problem captures the network dynamics and makes possible temporal regulation of the metabolic network. Through linearization of nonlinear constraints, this framework is based on the linear optimization problem which saves on computation time especially in a bilevel structure. A case study involving batch fermentation of Escherichia coli for ethanol production is considered to find an optimal manipulation strategy of metabolic networks for maximal productivity.

| 12:00-14:00 | TuPP.5 |
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*Finding Targets for Genome Reduction in Streptomyces Lividans TK24 Using Flux Balance Analysis*

| Daniels, Wouter | KU Leuven |
| --- | --- |
| Bouvin, Jeroen | KU Leuven |
| Busche, Tobias | Bielefeld Univ. |
| Kalinowski, Jörn | Bielefeld Univ. |
| Bernaerts, Kristel | KU Leuven |

A genome reduction can be a good starting point for optimizing a wild-type strain for use in an industrial process. The complex soil bacterium *Streptomyces lividans* TK24 produces many compounds that can hinder the industrial objective. Genome reduction is often based on phylogenetic conservation and absolute gene expression values. Here, flux balance analysis is proposed as an additional and complementary method for identifying potential targets for genome reduction. The effect of deletions of (blocks of) metabolic genes on bacterial growth is simulated in a high throughput fashion. Targets identified through this method show lower gene expression and are less likely to be conserved between different *Streptomyces* strains. Gene expression data are used for assessing the effect of gene deletions in silico to improve prediction accuracy.

| 12:00-14:00 | TuPP.6 |
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*Extraction of Physiological State Functions in Heterogeneous Cell Population Models*

| Hussain, Mubashir | Friedrich-Alexander Univ. Erlangen-Nürnberg |
| Waldherr, Steffen | KU Leuven |

A simple yet generic approach is presented to extract the growth and breakage kinetics from the temporal data of heterogeneous cell population. The moment form of the one-dimensional population balance equation is directly solved by a MATLAB solver for linear systems to extract the kinetics. The corresponding systems of linear equations are, however, highly underdetermined and ill-conditioned. To address this, the problem is regularized by assuming a suitable upper bound of the solution. The range between minimum and maximum possible values of the solution is discretized into several sub-intervals. The system is then solved against each sub-interval, whose values are used as lower and upper bounds in a suitable MATLAB solver and a local solution is obtained in all these ranges. The final solution is then computed by taking average of all solutions having residual norms less than a particular threshold. To validate the method, the results of the inverse technique are compared and discussed against two theoretical experiments.

| 12:00-14:00 | TuPP.7 |

*Quantitative Comparison of Competing PDE Models for Pom1p Dynamics in Fission Yeast*

| Hross, Sabrina | Helmholtz Zentrum München |
| Fiedler, Anna | Tech. Univ. München |
| Theis, Fabian J. | Helmholtz Zentrum München |
| Hasenauer, Jan | Helmholtz Zentrum München |

Gradient formation of Pom1 is a key regulator of cell cycle and cell growth in fission yeast (Schizosaccharomyces pombe). A variety of models to explain Pom1 gradient formation have been proposed, a quantitative analysis and comparison of these models is, however, still missing. In this work we present four models from the literature and perform a quantitative comparison using published single-cell images of the gradient formation process. For the comparison of these partial differential equation (PDE) models we use state-of-the-art techniques for parameter estimation together with model selection. The model selection supports the hypothesis that buffering of the gradient is achieved via clustering. The selected model does, however, not ensure mass conservation, which might be considered as problematic.

| 12:00-14:00 | TuPP.8 |

*A Comparative Analysis of Dynamic Models of the Central Carbon Metabolism of Eschericha Coli*

| Lima, Ana Patricia | Univ. of Minho |
| Baixinho, Vitor | Univ. of Minho |
| Machado, Daniel | Univ. of Minho |
| Rocha, Isabel | Univ. of Minho |

Dynamic models of metabolism have been developed for a variety of systems and can be applied in metabolic engineering design and to understand the time-varying characteristics of the systems when exposed to different stimuli. Hereby we analyse and compare the most used and complete kinetic models available for the central carbon metabolism of *E. coli*. Stoichiometric and kinetic comparisons showed several differences, discrepancies and incoherence especially regarding the kinetic mechanisms assumed, parameters and units. Time course and steady-state simulations and also comparison with an experimental dataset put in evidence major differences regarding responses to the same stimulus. The results presented raise important questions regarding the need of using standard methodologies in dynamic model construction as well as in using experimental data for model validation.

| 12:00-14:00 | TuPP.9 |

*A Supplemental Treatment for Chemotherapy: Control Simulation Using a Mathematical Model with Estimated Parameters Based on in Vivo Experiment*

| Paryad-zanjani, Sasan | Univ. of Tehran |
| Mahjoob, Mohammad J. | Univ. of Tehran |
| Amanpour, Saeid | Cancer Biology Res. Center, Tehran Univ. of Medical Sciences |
| Kheirbakhsh, Raheleh | Cancer Biology Res. Center, Tehran Univ. of Medical Sciences |
| Haji Akhoundzadeh, Mehran | Cancer Biology Res. Center, Tehran Univ. of Medical Sciences |

Combinations of experimental studies and theoretical models have always played a key role in the clinical development of cancer treatments. In this study, in-vivo experiments are conducted in order to study the effects of DDW on melanoma tumor growth and its pharmacokinetics. Existing mathematical models are then employed to describe the melanoma dynamics and drug effects on the tumor growth. The model includes the tumor growth, chemotherapy, and pharmacokinetics. The model parameters are computed by fitting the mathematical relations to the test data using genetic algorithm (GA). A SDRE (State Dependent Ricatti Equation) based control strategy is then synthetized that leads to promising results. An optimal treatment plan is obtained consisting chemotherapy and DDW as a supplement treatment.

| 12:00-14:00 | TuPP.10 |

*Metabolomics and Network Biology: Sex Comparative Analysis of Mouse Brain Regional Metabolic Physiology*

| Vasilopoulou, Catherine G. | Univ. of Patras |
| Margarity, Marigoula | Univ. of Patras |
| Klapa, Maria | Univ. of Maryland |

Mammalian brain is considered the most complex and multi-scale organ of the body. However, its biochemistry is not extensively studied and there is need for a systemic and systematic investigation in the context of variation among brain regions and between sexes. Towards that, systems biology, and especially metabolomics, allowed neuroscientists to move from the study of individual molecules or circuits to a systems-level perspective of the complexity of brain metabolism. Additionally, network and systems biology have contributed greatly to the attempt of reconstruction an accurate metabolic network activity map. Given that, we present in this work the value of studying brain central carbon metabolism in the context of metabolic network reconstruction using metabolomics. More specifically, the aim of this work is to study the metabolic physiology of brain, based on the comparative analysis of the metabolic profile of male and female Balb-c/J mice in three brain regions, i.e. cortex, midbrain and hippocampus, using GC-MS metabolomics. Our results demonstrate the significant variation in the metabolic profiles between the various brain regions and between sexes, confirming the need for this variation to be considered in the interpretation of the brain metabolomic data.

| 12:00-14:00 | TuPP.11 |

*Streamlining GC-MS Metabolomic Analysis Using the M-IOLITE Software Suite*

| Maga-Nteve, Christoniki | Univ. Patras |
| Klapa, Maria | Univ. Patras |

Metabolomics, as a rapidly growing omic analysis, has being used extensively to explore the dynamic response of biological systems in several diseases/disorders and contexts. Therefore, it has become commonplace in a wide variety of disciplines and there is an intense need for development of software suites that provide the user with a less complicated and invalid analysis. These suites must integrate meta-analysis, a standardized data normalization method and a safe repository for all types of biological samples. In the case of the Gas Chromatography-Mass Spectrometry (GC-MS) metabolomics, due to the complexity of the analysis, multiple procedures that are essential for the metabolite identification

require special manipulation. Moreover, metabolomic analysis produces a vast amount of unidentified compound data, so there is a need for unknown peak identification methods. While a number of tools offer access to datasets, constantly providing new releases for data processing and the fact that considerable progress has been made in that area, there is no computational platform that emerges as a standardized approach which includes specialized normalization methods for GC-MS metabolomic analysis and incorporates the metabolic network analysis into data interpretation and unknown peak identification. To address these issues, as the datasets obtained from metabolomics experiments still remain extremely large and dense, we have implemented M-IOLITE, a computational suite for the efficient and automatic analysis of high-throughput metabolomic experiments. The aim of the suite is to streamline GC-MS metabolomic data analysis and to reduce complexity enabling the use of a friendly interface for processing, validating and annotating data. It integrates specialized normalization methods, a safe data repository and a peak library providing through its pipeline a useful tool which enables rapid and accurate analysis of the metabolomic profiles into an interactive system.

| 12:00-14:00 | TuPP.12 |

*Towards Robust, High-Performance Production Strains: Constrained-Based Identification of Strain Designs Leading to an Optimally Growth-Coupled Product Synthesis*

| Alter, Tobias Benedikt | RWTH Aachen Univ |
| Ebert, Birgitta Elisabeth | RWTH Aachen Univ |
| Blank, Lars M. | RWTH Aachen Univ |

A bio-based economy is strongly dependent on efficient processes utilising robust, high-performance production strains. For the generation and improvement of such strains, one major goal is to metabolically couple product synthesis to microbial growth. Growth-coupling enforces production in fermentation processes and simultaneously ensures high and stable production characteristics. In the specific case of target compound production via synthetic pathways, growth-coupling is not only advantageous but necessary to avoid downregulation of the artificially integrated metabolic routes. With regard to the complexity of metabolic networks, model-based systems metabolic engineering approaches aid in predicting reaction or gene deletions enabling a growth-coupled target compound production.

In this work, a novel constrained-based tool, named gcOpT, was developed for the identification of knockout-based strain designs that particularly lead to optimal growth-coupling characteristics. At the same time, gcOpT accounts for high productivities of the target compound to facilitate the establishment of economically feasible processes. The principle of gcOpT is to maximise the minimal guaranteed production rate for a fixed medium growth rate, hence leading to an optimisation of minimal guaranteed yields for the whole range of accessible growth states. The functionality of gcOpT was validated by optimising ethanol production in an Escherichia coli model. In contrast to other previously published optimisation tools, gcOpT identified reaction deletions that both guarantee a strictly enforced production of ethanol and adequate maximal growth rates, thus high productivities.

gcOpT was applied to identify intervention strategies which growth-couple the production of the biofuel 2-butanone in Pseudomonas putida KT2440. The respective simulations were based on the genome-scale metabolic model iJP962. Several strategies with different numbers of reaction deletions as well as expression of de-novo reactions were predicted, which enforce production of 2-butanone on a glucose-based minimal medium.

| 12:00-14:00 | TuPP.13 |

*A Dynamic Model of Growth and Metabolism of AGE1.HN Suspension Cells*

| Ramos, Joao | Max Planck Inst |
| Reichl, Udo | Max Planck Inst. for Dynamics of Complex Tech |
| Rath, Alexander Georg | ONCOTEC Pharma Produktion GmbH |
| Genzel, Yvonne | Max Planck Inst. for Dynamics of Complex Tech. Systems |
| Sandig, Volker | ProBioGen AG |
| Rose, Thomas | ProBioGen AG |

Biological process optimization relies on the understanding of the highly complex cellular metabolism. Overcoming this challenge requires a combination of mathematical approaches and experimental methods. Here, s imilar to a previous model established for adherent MDCK cells (Rehberg, 2013), we formulate a mechanistic mathematical model for AGE1.HN suspension cells (a human parental cell line) designed to produce recombinant proteins as well as virus. Therefore, we coupled a segregated model for growth, which successfully describes viable cell concentration, diameter changes as well as substrate and metabolic product dynamics with a structured model for intracellular metabolite dynamics (key reactions of glycolysis, citric acid cycle, glutaminolysis and pentose phosphate pathway). The developed model uses either first order, Michaelis Menten reversible/irreversible or hill kinetics and was validated against three different batch experiments. We elucidate the increase of hexokinase activity caused by gene transcription regulated by the available glucose, and found a peak-like increase in intracellular concentration of fructose-1,6-bisphosphate due to growth-dependent activity of the aldolase enzyme. This model could be used to gain a deeper insight into the control of growth and metabolism of this suspension cell line under various cultivations conditions.

| 12:00-14:00 | TuPP.14 |

*New Methods for Modeling of Microbial Communities with Stoichiometric Metabolic Models*

| Koch, Sabine | Max Planck Inst. for Dynamics of Complex Tech. Systems |
| Benndorf, Dirk | Otto Von Guericke Univ. Magdeburg |
| Reichl, Udo | Max Planck Inst. for Dynamics of Complex Tech |
| Klamt, Steffen | Max Planck Inst. for Dynamics of Complex Tech. Systems |

Microbial communities play a major role in ecology, medicine and various industrial processes. Modeling can help to gain a better understanding of interactions in the community and factors that influence the community. In this work we used stoichiometric metabolic models to investigate interactions and the community structure of microbial communities for biogas production. Model organisms representing different degradation steps in anaerobic digestion are *Desulfovibrio vulgaris*, *Methanococcus maripaludis*, *Methanosarcina barkeri*, *Clostridium acetobutylicum*, *Syntrophomonas wolfei*, *Escherichia coli* and *Acetobacterium woodii*. The investigated communities consisted of two to seven of these organisms.

We used two different approaches to model communities, both assuming equal growth rates for all organisms. In the first approach we used flux balance analysis to first maximize the community growth rate and then, as secondary objective, the biomass yields of all organisms. With this method we investigated the influence of different substrates as well as the ATP maintenance coefficient on predicted community compositions of a two-species community. The simulation results showed that the ATP maintenance coefficient influences the community compositions especially for low growth rates and if the maintenance coefficients differ between the organisms. The community composition also depends on the substrate used by the community. For a three-species community exchangeability and essentiality as well as methane yields and specific methane production rates were predicted.

In the second approach we computed first bounded elementary vectors from the single-species models and chose those vectors with maximum biomass yields as building blocks for a community model. The latter is then analyzed by its elementary flux modes. This method reduced the computation times for investigation of the

community models considerably and enabled us to study complex communities consisting of up to seven organisms. As one result, the simulation results reflected the expected ratio of 50% $CO_2$ and 50% methane in the biogas with glucose as a substrate.

| 12:00-14:00 | TuPP.15 |
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*Genome-Scale Modeling Approach for in Silico Analysis of CHO Cell Metabolic Network*

| Calmels, Cyrielle | UCB and DTU |
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| Andersen, Mikael Rørdam | Tech. Univ. of Denmark |
| Malphettes, Laetitia | UCB Pharma S.A., Belgium |

| 12:00-14:00 | TuPP.16 |
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*Model-Based Metabolic Engineering of Escherichia Coli for High Yield Itaconic Acid Production*

| Harder, Björn-Johannes | Max Planck Inst. for Dynamics of Complex Tech. Systems |
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| Bettenbrock, Katja | Max Planck Inst. for Dynamics of Complex Tech. Systems |
| Klamt, Steffen | Max Planck Inst. for Dynamics of Complex Tech. Systems |

Itaconic acid has been recognized as a high potential platform chemical that can be synthesized by bio-based production processes. To enable high-yield itaconic acid production by Escherichia coli, we iteratively determined intervention strategies (constrained Minimal Cut Sets) restricting the solution space to flux vectors with high itaconic acid yield (> 0.7 mol/mol) at all growth rates. In each iteration step, the stoichiometric network model was adjusted to the metabolic behavior (by-product formation) of the current deletion strain. After three iterations and the implementation of 5 reaction knockouts we achieved a high itaconic acid yield of 0.77 mol/(mol glucose) in Minimal Medium with supplementation of small amounts of glutamic acid. In a fed-batch bioreactor cultivation the titer was increased to 32 g/l compared to 2.2 g/l in shake flask cultivations. These are by far the highest yields and titers ever reported for the heterologous itaconic acid production.

| 12:00-14:00 | TuPP.17 |
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*Design Principles As a Guide for Metabolic Engineering: Application to Halophiles*

| Sehr, Christiana | Tech. Univ. München |
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| Kremling, Andreas | Tech. Univ. München |
| Marin-Sanguino, Alberto | Tech. Univ. München |

ABSTRACT

Biotechnology would benefit considerably if there were a wider diversity of microoorganisms available for industrial use. The characterization of non-standard microorganisms, however is an important challenge. Widely used microorganisms like E. coli have been studied for more than a century, the incorporation of additional organisms to industry would have to proceed much faster. This can in part be achieved using high throughput methods to collect information and using the theoretical framework that has been developed through the study of model organisms.

Although specific details are very seldom generalizable between biological systems, there are certain patterns that get observed repeatedly in very different organisms. These patterns are often called design principles and their recurrence can be explained by them being reusable solutions to commonly occurring problems in an evolutionary context -- e.g. end-product inhibition as a way to ensure responsive biosynthetic pathways. By finding and analyzing design principles we can not only understand how evolution has molded the characteristics of certain metabolic pathways but also find rational modification strategies that shift the performace of the system to achieve different goals. We will present some examples on the concept of design principles has been valuable in our research on the industrial performance of Halomonas elongata

| 12:00-14:00 | TuPP.18 |
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*Fast Reconstruction of Context-Specific Metabolic Models and Omics Integration*

| Pires Pacheco, Maria | Univ. of Luxembourg, |
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| Vlassis, Nikos | Adobe Res. 345 Park Ave, San Jose, CA, USA |
| John, Elisabeth | Univ. of Luxembourg |
| Kaoma, Tony | Genomics Res. Unit, LIH, L-1526 Luxembourg, Luxembourg |
| Heinäniemi, Merja | Univ. of Eastern Finland |
| Nicot, Nathalie | Genomics Res. Unit, LIH, L-1526 Luxembourg, Luxembourg |
| Vallar, Laurent | Genomics Res. Unit, LIH, L-1526 Luxembourg, Luxembourg |
| Bueb, Jean-Luc | Univ. of Luxembourg |
| Sinkkonen, Lasse | Univ. of Luxembourg |
| Sauter, Thomas | Univ. of Luxembourg |

Context specific models, which were shown to be very powerful for the integration and analysis of omics data, might be applied for precision medicine as a diagnostic tool tailored to the analysis of group of patients. The use of algorithms as tool for the routine analysis of metabolic diseases require fast algorithms with a high level of predictive power, robustness to noise and sensitivity. FASTCORE1, which is devoid of heuristic parameters, allows building of high-quality context-specific models in the time order of seconds. FASTCORE uses an approximation of the cardinality function to force the core reactions set to carry a flux above a user-defined threshold $\varepsilon$. Then it applies L1-minimization to penalize the activation of reaction with low confidence level while constraining the set of core reactions to carry a flux. In order to cope with the non-negligible amount of noise associated with microarray experiments, FASTCORE was extended to FASTCORMICS2. FASTCORMICS uses Barcode to identify active and inactive reactions based on solid statistical evidences. The prediction power, robustness and sensitivity of FASTCORE and FASTCORMICS along with 5 competing algorithms were assessed with a benchmarking workflow which revealed that all algorithms, with exception of FASTCORE and FASTCORMICS, failed to capture metabolic differences between tissues4.

We now extended the workflow to use RNA-seq data as input data. We built 10005 tumors and healthy models that allowed identifying tumour-specific reactions signatures that might be used as potential drug targets (AUC 97%).

1. Vlassis, N. et al. Fast reconstruction of compact context-specific metabolic network models. PLoS Comput. Biol. 10, e1003424 (2014). 2. Pacheco, M. P. et al. Integrated metabolic modelling reveals cell-type specific epigenetic control points of the macrophage metabolic network. BMC Genomics (2015). 3. McCall M. N. et al. The Gene Expression Barcode: leveraging public data repositories to begin cataloging the human and murine transcriptomes. Nucleic Acids Res. 39, D1011–D1015 (2011). 4. Pacheco, M. P. et al . Benchmarking procedures for high-Throughput context Specific Reconstruction Algorithms. Front. Physiol. Front. Physiol 6, (2016).

| 12:00-14:00 | TuPP.19 |
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*The Influence of EGFR/Met Receptor Abundance on Therapy Resistance in Non-Small Cell Lung Cancer Cell Lines*

| Hass, Helge | Albert-Ludwigs Univ. Freiburg |
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| Salopiata, Florian | DKFZ Heidelberg |
| Kreutz, Clemens | Albert-Ludwigs Univ. Freiburg |
| Klingmüller, Ursula | DKFZ Heidelberg |
| Timmer, Jens | Albert-Ludwigs Univ. Freiburg |

Lung cancer is one of the most frequent cancer types and, despite advances in personalized medicine, still exhibits serious outlook due to high mutation rate, early spread and formation of therapy resistance. Systemic therapies with epidermal growth factor

receptor (EGFR) tyrosine kinase inhibitor (TKI) treatment lead to only a few months increased survival due to resistance formation. Apart from EGFR mutations, amplification of the hepatocyte growth factor (HGF) is supposed to bypass TKI treatment. Yet, the mechanism of this EGF/HGF-mediated resistance remains unknown. In this study, time resolved quantitative data for EGF and HGF induced signal transduction was acquired in NSCLC cell lines. Further, a mechanistic dynamic pathway model based on ordinary differential equations was developed to gain insights into mechanisms regulating the interaction of the receptors and their crosstalk. After parameter estimation via a multi-start, gradient-based optimization, the model suggested an important role of abundance and ratio of EGF and Met receptors for the formation of sustained heterodimers between both. With this, distinct phosphorylation dynamics of the receptors and several downstream targets of the MAP-kinase and PI3-kinase are well described in two cell lines harboring different receptor expression levels on the cell surface. Accordingly, experiments with EGFR TKIs, receptor overexpression in the available cell lines and the analysis of receptor degradation kinetics supported model predictions made by profile likelihood-based prediction bands. With this strategy, a novel approach can be applied to predict the clinical outcome of applied therapies and to develop strategies to avoid the emergence of therapy resistance, which was recently consolidated in a published clinical study.

| 12:00-14:00 | TuPP.20 |
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*Energy, Coupled Oscillators & Epilepsy*

| O'Sullivan-Greene, Elma | The Univ. of Melbourne |
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| Gawthrop, Peter | Univ. of Glasgow |
| Mareels, Iven | The Univ. of Melbourne |

Introduction: Epilepsy, a dynamic disease of the brain, is characterized by recurrent seizure episodes. Epileptic seizures are associated with brainwaves that have synchronous and high energy (large amplitude) electric field activity. Clinical hypothesis for epileptic seizures include: seizures occur to dissipate excess energy in the cortex; seizures are a massive deployment of energy to protect or reset the brain; seizure termination dynamics are primarily dependent on a depletion of the available system energy. Yet existing models for networks of neurons do not explicitly consider energy. Incorporating energy dynamics into neural models, in particular to understand the role of energy in neural synchrony, may provide new insight into epilepsy. Methods: We examine the impact of energy supply disruption on synchronized coupled oscillators (an abstract model for synchronizing and oscillatory neural dynamics). Results: The results illustrate that the level of desynchrony correlates to the fractional energy shortfall and the duration over which the shortfall was maintained. Discussion: This simplistic simulation study illustrates that energy supply plays a central role in de-synchronizing behavior in coupled oscillators. This highlights the need for an energy approach to neural oscillation modeling to understand the key role that supply energy, as a function of available Adenosine triphosphate (ATP), may play in maintenance of synchronous epileptic seizure activity and cessation of seizures.

| 12:00-14:00 | TuPP.21 |
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*A Single Catastrophic Genomic Event Is Rate Limiting the Development of Osteosarcoma*

| Bilke, Sven | National Cancer Inst |
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Over sixty years ago, the groundbreaking works by Nordling1953 and Armitage & Doll developed the somatic mutation theory of cancer. It suggested a deep connection between the age dependent incidence rates of cancer with elementary mutational processes in cancer. However, their method to estimate the number of driver mutations from the characteristic increase of adult cancer risk with patient age implicitly assumes tissue homeostasis. It can therefore not be used for developmental cancers emerging from growing, non-homeostatic tissues. Here we extend their model by integrating a growth model to analyze pediatric malignancies. Using Osteosarcoma (OS) as an example, we show how this type of effective models can be used to gain insight into the etiology of OS. We find that as single event is rate

limiting for cancerogenesis and that the disease develops almost entirely independently from environmental contributions in the general population.

| 12:00-14:00 | TuPP.22 |
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*Sepsis Leads to Reduced Variability of Gene and Isoform Expression*

| Biering, Antje | Hans Knöll Inst. (HKI) |
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| Roell, Daniela | Jena Univ. Hospital |
| Giszas, Benjamin | Jena Univ. Hospital |
| Fang, Haoshu | Jena Univ. Hospital |
| Schindler, Claudia | Jena Univ. Hospital |
| Groth, Marco | Fritz Lipmann Inst. Leibniz Inst. for Age Res. (FLI) |
| Claus, Ralf | Jena Univ. Hospital |
| Dahmen, Uta | Jena Univ. Hospital |
| König, Rainer | Jena Univ. Hospital |

Sepsis is a potentially fatal systemic infection with multiple organ failure. To show that sepsis reduces variability of isoforms, gene expression and gene variety, we investigated transcript levels of septic and non-septic samples and found reduced coordinated alternative splicing, a reduced number of genes with detectable gene expression, and a considerable higher number of down compared to up regulated genes. Instead of treatments focussing only on dampening the exaggerated immune response we suggest to rather remodel the expression program back to a well-balanced homeostasis between activation and regeneration of the immune cells.

| 12:00-14:00 | TuPP.23 |
|---|---|

*Model-Based Genotype-Phenotype Mapping Used to Investigate Gene Signatures of Immune Sensitivity and Resistance in Melanoma Micrometastasis*

| Lai, Xin | Erlangen Univ. Hospital |
|---|---|
| Santos Rosales, Guido | Univ. Nürnberg-Erlangen |
| Vera-Gonzalez, Julio | Univ. Erlangen |

In this study, we combined kinetic modelling and patient gene expression data analysis to elucidate biological mechanisms by which melanoma becomes resistant to the immune system and to immunotherapy. To this end, we systematically perturbed the parameters in a kinetic model and performed a mathematical analysis of their impact, thereby obtaining gene signatures associated with the emergence of phenotypes of melanoma immune sensitivity and resistance. Our phenotypic signatures were compared with published clinical data accounting for pretreatment tumor metagenes, which are annotated with standard gene ontology terms and subjected to immunotherapy against metastatic melanoma. Our method unravelled an intriguing mechanism by which melanoma may develop immunoresistance. In particular, the mechanism, by which micrometastases can minimize the combined anti-tumor activity of complementary responses mediated by cytotoxic T cells and natural killer cells, is caused by a signature showing intermediate expression levels for antigen-presentation associated genes. Furthermore, we simulated the model to test the efficacy of cytokines used as low-dose co-adjuvants for the therapeutic anticancer vaccine to overcome tumor immunoresistance.

| 12:00-14:00 | TuPP.24 |
|---|---|

*Prediction of Optimal Profiles for the Production of Monoclonal Antibodies Based on Identified Growth Phases and Key Metabolites*

| Heinzle, Elmar | Saarland Univ |
|---|---|

Fed-batch cultures of Chinese Hamster Ovary (CHO) cells are a major workhorse for the production of biopharmaceuticals especially of monoclonal antibodies. We propose a systematic approach to identify metabolic phases and get an accurate predictive model of cell metabolism during CHO fed-batch culture. First, experimental data are collected from 2 L lab-scale cultures

covering a desired experimental space. To this end, we applied the metabolic steady state concept and used a linear piecewise regression. The external metabolite rates are expressed as a linear function of the specific growth rate. The resulting macroscopic model is relatively simple but with a high predictive power and does not require a detailed mechanistic metabolic model that would be very complex and laborious to establish. Using the model structure and parameter values from a small scale cell culture (2 L) training data set, it was possible to predict metabolic rates of new fed-batch cultures by using the experimental specific growth rate in both 2 L and 2000 L scales. In a next step a fully predictive cell growth model was established by incorporating growth kinetics for the identified phases. That cell growth model combined to a linear piecewise regression model of cell metabolism allows us to predict the impact of an untested feeding strategies on cell culture performance.

| 12:00-14:00 | TuPP.25 |
|---|---|

*Modelling Mixautrophic Growth of Chlorella with Four Organic Substrates*

| Anais, Bacquet | UPMC, Sorbonne Univ |
| Baroukh, Caroline | INRA |
| Steyer, Jean-Philippe | INRA |
| Bernard, Olivier | INRIA |

A metabolic model has been developed to represent the mixautrophic growth of different strains of Chlorella on a blend of substrates including acetate, butyrate, glucose and glycerol, with or without additional light. The model was calibrated and compared to 138 different experiments, with a very good prediction capability. The model was then used to find the optimal mixture of low cost substrates to add to the process in order to wave the inhibitory effect of butyrate.

| 12:00-14:00 | TuPP.26 |
|---|---|

*Thermodynamically Constrained Averaging Theory for Cancer Growth Modelling*

| Albrecht, Marco | Univ. of Luxembourg |
| Sciumè, Giuseppe | Univ. of Bordeaux |
| Lucarelli, Philippe | Univ. of Luxembourg |
| Sauter, Thomas | Univ. of Luxembourg |

In Systems Biology, network models are often used to describe intracellular mechanisms at the cellular level. The obtained results are difficult to translate into three dimensional biological systems of higher order. The multiplicity and time dependency of cellular system boundaries, mechanical phenomena and spatial concentration gradients affect the intercellular relations and communication of biochemical networks. These environmental effects can be integrated with our promising cancer modelling environment, that is based on thermodynamically constrained averaging theory (TCAT). Especially, the TCAT parameter viscosity can be used as critical player in tumour evolution. Strong cell-cell contacts and a high degree of differentiation make cancer cells viscous and support compact tumour growth with high tumour cell density and accompanied displacement of the extracellular material. In contrast, dedifferentiation and losing of cell-cell contacts make cancer cells more fluid and lead to an infiltrating tumour growth behaviour without resistance due to the ECM. The fast expanding tumour front of the invasive type consumes oxygen and the limited oxygen availability behind the invasive front results automatically in a much smaller average tumour cell density in the tumour core. The proposed modelling technique is most suitable for tumour growth phenomena in stiff tissues like skin or bone with high content of extracellular matrix.

| 12:00-14:00 | TuPP.27 |
|---|---|

*Set-Based Experiment Design for Model Discrimination Using Bilevel Optimization*

| Rudolph, Nadine | OvG Univ. Magdeburg |
| Streif, Stefan | Tech. Univ. Chemnitz |
| Findeisen, Rolf | OvG Univ. Magdeburg |

Experiment design can be used to discriminate between valid and invalid models. This task is not trivial as models are typically nonlinear and the kinetic parameters and initial conditions are uncertain. In this work, we propose a set-based and bilevel optimization approach to design an input sequence such that nonlinear models with uncertainties can be discriminated with guarantees based on a single measurement. In the outer program of the bilevel optimization program, an input minimizing a given norm and satisfying input constraints is determined. For the determined input sequence, the inner program certifies that the reachable output sets of the models are nonoverlapping at a chosen time-point, thus guaranteeing model discrimination. To be able to provide guarantees despite the nonconvexities of the reachable sets, we convexify the inner program. We demonstrate our approach at the chemostatic signaling system of *Dictyostelium discoideum*.

| 12:00-14:00 | TuPP.28 |
|---|---|

*Control of a Class of Large-Scale Boolean Networks for Biological Systems Using Constant Inputs*

| Yang, Jung-Min | Kyungpook National Univ |
| Cho, Kwang-Hyun | Korea Advanced Inst. of Science and Tech. (KAIST) |

Boolean networks can describe dynamics of genetic and cellular networks in a simple and abstract framework. This paper presents a constant control scheme for stabilization of large-scale Boolean networks. A number of state nodes are selected as constant control inputs so that the Boolean network can reach desirable attractor or cycles. Strongly connected components of the Boolean network are considered to reduce the computational cost. A simulation study on the problem of determining combinatorial targeted drugs for desired cellular phenotype is provided.

| 12:00-14:00 | TuPP.29 |
|---|---|

*The Chemical-Transcriptional Landscape of Small Molecules*

| Sirci, Francesco | TIGEM |
| Napolitano, Francesco | TIGEM |
| Carrella, Diego | TIGEM |
| di Bernardo, Diego | TIGEM |

| 12:00-14:00 | TuPP.30 |
|---|---|

*Modeling of Biomass Composition Using Dynamic Flux Balance Analysis for Optimization of Microalgal Biorefineries*

| Flassig, Robert J | Max Planck Inst. for Dynamics of Complex Tech. Systems |
| Fachet, Melanie | Max Planck Inst. for Dynamics of Complex Tech. Systems |
| Gladebeck, Steffie | Max Planck Inst. for Dynamics of Complex Tech. Systems |
| Pirwitz, Kristin | Max Planck Inst. for Dynamics of Complex Tech. Systems |
| Rihko-Struckmann, Liisa | Max Planck Inst. for Dynamics of Complex Tech. Systems |
| Sundmacher, Kai | Max Planck Inst. for Dynamics of Complex Tech. Systems |

Photosynthetic microorganisms such as cyanobacteria and microalgae are innovative cell factories for sustainable production of valuable products from renewable feedstocks. The broad scope of application for microalgal compounds includes the feed, food, bioenergy and biochemical sector. The content of high-value products, such as carotenoids or polyunsaturated fatty acids, in the biomass is typically low and a large fraction of residual biomass remains unused. In contrast, the economic feasibility is often difficult to achieve because of energy and cost-intensive harvesting and extraction steps. Therefore, microalgal process design requires tailor-made downstream processing strategies and a biorefinery approach to valorize most of the biomass fractions. In this contribution we present a modeling approach that

quantitatively describes various biomass fractions in the green alga Dunaliella salina, the most important organism for industrial β-carotene production. The approach is based on Dynamic Flux Balance Analysis (DFBA) and underlying metabolic network is based on the well-established genome-scale network reconstruction of the model organism Chlamydomonas reinhardtii. The DFBA model provides a detailed mechanistic description of the intracellular stoichiometry and metabolite accumulation in combination with changes in the extracellular environment. This provides a structured dynamic model that predicts growth, metabolic activity and biomass composition in a dynamic bioreactor environment.

| 12:00-14:00 | TuPP.31 |
|---|---|

*Identification and Regression Based on Martingale Dynamics*

| Mau, Jochen | Iqmeth - Inst. Für Quantitative Methodik |
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In repeated observation of a technical or biological process, traditional methods of statistical analysis that are multivariate in the sequence of measurement times, are inadequate. To properly distinguish between past, present and future, a modern probabilistic approach is required. While estimation follows simple concepts, regression modelling of continuous responses needs a more complicated approach via marked point processes. Principal concepts and reasoning are explained without mathematical rigor or recourse on samples of independent observations.

| 12:00-14:00 | TuPP.32 |
|---|---|

*Efficient Simulation of Heterogeneity and Stochasticity in Microbial Processes*

| Pischel, Dennis | OvG. Univ. Magdeburg |
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| Flassig, Robert J | Max Planck Inst. for Dynamics of Complex Tech. Systems |
| Sundmacher, Kai | Max Planck Inst. for Dynamics of Complex Tech. Systems |

In this contribution we focus on the efficient simulation of microbial systems containing variability of the initial protein concentration, external fluctuations and probabilistic biochemical reactions. The exact solution, which captures the dynamics of these systems, is derived by the chemical master equation. The most popular technique to solve the chemical master equation relies on Monte Carlo techniques being computational very intense. To overcome this difficulty a new method is proposed, which uses a hybrid approach consisting of the sigma point method to capture the variability of the initial protein concentration as well as environmental fluctuations and the $\tau$-leaping algorithm to account for the probabilistic reactions. This frame work enables us to efficiently simulate stochastic biochemical systems containing various sources of noise and estimate via optimization unknown parameters.

| **TuKA1P** | Nave |
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| **Pablo Iglesias** (Keynote Session) | |
| Chair: Jayawardhana, Bayu | Univ. of Groningen |

| 14:00-14:30 | TuKA1P.1 |
|---|---|

*The Regulation of Cell Motility through an Excitable Network*

| Bhattacharya, Sayak | Johns Hopkins Univ |
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| Iglesias, Pablo A. | Johns Hopkins Univ |

Recent years have demonstrated that the actin cytoskeleton and other signaling elements in motile cells have many of the hallmarks of an excitable medium, including the presence of propagating waves, a refractory period, as well as a threshold for activation. Here we show how these behaviors can be explained by the presence of a signal transduction excitable network that integrates a number of signals and coordinates actin polymerization. In this model, spontaneous triggering of the excitable network accounts for the random migration of unstimulated cells. Moreover, internal and external signals both

chemical and mechanical bias excitability spatially, thus providing a means by which cell motility is directed towards spatial cues. We also show how the model predicts that the set point of the excitable system can be altered by changing the threshold.

| **TuKA2P** | Nave |
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| **Jörg Stelling** (Keynote Session) | |
| Chair: Rolf Findeisen | OvG Univ. Magdeburg |

| 14:30-15:00 | TuKA2P.1 |
|---|---|

*Identification of Predictive Dynamic Models for Systems Biology*

| Stelling, Joerg | ETH Zurich |
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| **TuA1** | Nave |
|---|---|
| **Special Session in Memoriam of Peter Wellstead** | |
| Chair: Henson, Michael A. | Univ. of Massachusetts, Amherst |
| Co-Chair: Bullinger, Eric | OvG Univ. Magdeburg |

| 15:20-15:40 | TuA1.1 |
|---|---|

*Peter Wellstead and the Me-We Principle of Life*

| Wolkenhauer, Olaf | Univ. Rostock |
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A complicated system consists of many and a great variety of components, whose interactions may also be difficult to observe. A complex system is characterised by nonlinear spatio temporal interactions of the systems's components. Living systems are complicated, complex, and unique in that every component owes its presence to the agency of all the remaining components, and also exists for the sake of the others: The whole and its parts reciprocally produce each other; determine the functioning of each other. Control engineers know how to use mathematical modelling and simulation to study complex systems and so it is not surprising that they were drawn into the development of systems biology approaches in molecular and cell biology. I was fortunate enough to join this movement from 1997 onwards and my career path was made possible by the late Peter Wellstead. He was not my supervisor and yet he supported me in many ways. Today, I would argue that Peter realised that a research team is a living system, one in which the "Me" and "We" are tightly connected. Peter Wellstead cared about the people around him, showed interest and supported them generously, not in the usual sense but in the way that sees everyone being part of a larger whole. Once we realise that our research, our careers and lifes are governed by the Me-We principle, we can not only achieve better science but also become better people.

| 15:40-16:00 | TuA1.2 |
|---|---|

*A Reaction-Diffusion Model for the Progression of Parkinsons Disease*

| García, Míriam R. | IIM-CSIC |
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| Cloutier, Mathieu | Ec. Pol. De Montreal |
| Wellstead, Peter | NUI Maynooth |

The temporal and spatial development of Parkinsons disease has been characterised as the progressive formation of alfa-synuclein aggregations through susceptible neuronal pathways. We describe a new model for this progression mechanism in which Parkinsonian damage moves over time through the nervous system by the combined effect of the reaction kinetics of pathogenesis and molecular diffusion. In the reaction-diffusion model, the change from a healthy state to the disease state advances through the nervous system as a wave front of Parkinsonian damage, marking its path by accumulations of damaged alfa-synuclein and neurotoxic levels of oxidative species. Progression according to this model follows the most vulnerable routes through the nervous system as described by Braaks staging theory and predicts that damage will advance at differing speeds depending upon the level and number of risk factors, in a

manner that gives new insights into the variations with which Parkinsons disease develops.

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**16:00-16:20**      TuA1.3

*Gene Circuits for Self-Tuning Metabolic Pathways*

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| Oyarzún, Diego A. | Imperial Coll. London |

Here I will discuss our progress on gene circuits for dynamic control of metabolic pathways. In traditional engineered pathways, performance is limited by metabolic imbalances that impair growth. These imbalances arise from e.g. the accumulation of toxic intermediates, the depletion of key metabolites for survival, or the onset of native regulatory mechanisms that counteract pathway activity. We can overcome such limitations with genetic feedback circuits that adapt enzyme expression levels to the metabolic state of the host. When appropriately designed, genetic circuits cause a pathway to self-tune its expression levels and match production goals with a reduced burden on the host. In this talk I will review our work on genetic circuits to achieve pathway self-tuning, to control non-genetic variability, and to engineer multistable systems for large-scale multicellular circuitry. To conclude I will discuss our ongoing efforts to rewire metabolic regulation in E. coli with metabolite-responsive transcription factors, in collaboration with our experimental partners.

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**16:20-16:40**      TuA1.4

*Monotonicity of Kinetic Proofreading*

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| Kallies, Christian | OvG Univ. Magdeburg |
| Schliemann-Bullinger, Monica | OvG Univ. Magdeburg |
| Findeisen, Rolf | OvG Univ. Magdeburg |
| Lucia, Sergio | OvG Univ. Magdeburg |
| Bullinger, Eric | OvG Univ. Magdeburg |

This manuscript studies the monotonicity of multi-step ligand-receptor signalling motifs. Monotonicity with respect to parameters and state perturbations allow not only to exclude periodic solutions, but also to easily bound the responses in cases of bounded perturbations.

In classical coordinates, multi-step ligand-receptor signalling motifs are known not to be monotone. However, a generic coordinate transform allows for deriving conditions on the kinetic rate constants such that the signal is monotonously affected by perturbations to any one of the kinetic rate constants. The result is illustrated at the hand of a model of kinetic proofreading.

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**16:40-17:00**      TuA1.5

*On the Personalised Modelling of Cancer Signalling*

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| Fey, Dirk | Univ. Coll. Dublin |
| Kuehn, Axel | Univ. De Montpellier |
| Kholodenko, Boris N. | Univ. Coll. Dublin |

Dynamic modelling has long been used to understand fundamental principles of cell signalling and its dysregulation in cancer. More recently, these models have also been used to understand the individual risks of cancer patients, and predict their survival probabilities. However, the current methodologies for integrating tumour data and generating patient-specific simulations suffer from the lack of general applicability; they only work for cell signalling models in which only posttranslational protein modifications are considered, so that the total protein concentrations are conserved. Here, we present novel, generally applicable method. The method is based on a simple theoretical framework for modelling gene-regulation, and the indirect estimation of patient-specific parameters from tumour data. Because our method does not require time-invariance of the total-protein concentrations, it can be applied to models of any nature, including the many cancer signalling models involving gene-regulation.

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| **TuA2** | Gallery |
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| **Biotechnology Methods & Applications** (Regular Session) | |
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| Chair: Teusink, Bas | VU Univ. Amsterdam |
| Co-Chair: Klipp, Edda | Humboldt-Univ. Zu Berlin |

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**15:20-15:40**      TuA2.1

*Dynamic Metabolic Flux Analysis of Underdetermined and Overdetermined Metabolic Networks*

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| Fernandes, Sofia | Univ. of Mons |
| Robitaille, Julien | École Pol. De Montréal |
| Bastin, Georges | Univ. Catholique De Louvain |
| Jolicoeur, Mario | École Pol. De Montreal |
| Vande Wouwer, Alain | Univ. De Mons |

In this work, two metabolic networks representing the metabolism of CHO cells in fed-batch cultures are considered. The first metabolic network is relatively detailed and underdetermined with the available extracellular measurements, while the second is a reduced version of the former and is overdetermined. A dynamic metabolic flux analysis based on convex analysis (DMFCA) is applied to the detailed network, which allows the computation of the time evolution of bounded intervals. On the other hand, a linear optimization problem is solved for the reduced-size network, with either positivity constraints or box constraints inferred from DMFCA. In all cases, smoothing splines and mass balance differential equations are used to infer the time evolution of the uptake and excretion rates from experimental data. The analysis allows to get insight into CHO metabolism as well as to investigate the influence of the size of the metabolic network.

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**15:40-16:00**      TuA2.2

*Feasibility of Growth-Coupled Product Synthesis in Microbial Cell Factories*

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| Klamt, Steffen | Max Planck Inst. for Dynamics of Complex Tech. Systems |
| von Kamp, Axel | Max Planck Inst. for Dynamics of Complex Tech. Systems |
| Mahadevan, Radhakrishnan | Univ. of Toronto |

Growth-coupled product synthesis has become a key principle for metabolic engineering and various constraint-based modeling techniques have been developed to calculate intervention strategies by which a microorganism can only grow if it co-synthesizes a desired by-product. However, growth-coupled synthesis is not feasible for all metabolites.

Using geometric techniques we show which structural properties in a network are required such that biomass and product synthesis can be coupled at all. In networks without flux bounds, coupling is feasible if and only if an elementary mode exists that leads to formation of both biomass and product. Setting flux boundaries leads to more complicated inhomogeneous problems. Making use of the concept of elementary flux vectors, a generalization of elementary modes, criteria for feasibility of coupling can also be derived for this situation.

We used a core and a genome-scale metabolic model of E. coli and determined for each metabolite whether its net production can be coupled with growth by suitable reaction knockouts. The somewhat surprising result is that coupling is indeed possible for almost all metabolites (>95%) in both core and genome-scale model. I will also present a realistic application example where we designed and constructed an E. coli strain for high-yield production of itaconic acid.

Overall, our work (i) provides important insights for a central problem of computational strain design, (ii) proves that growth-coupled product synthesis is feasible for the great majority of metabolites in E. coli, and (iii) emphasizes elementary flux vectors as a valuable tool for metabolic pathway analysis in inhomogeneous systems.

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**16:00-16:20**      TuA2.3

*Multi-Physics Modeling of Light-Limited Microalgae Growth in Raceway Ponds*

| Nikolaou, Andreas | Imperial Coll. London |
| Booth, Peter | Imperial Coll. London |
| Gordon, Fraser | Imperial Coll. London |
| Yang, Junfeng | Imperial Coll. London |
| Matar, Omar | Imperial Coll. London |
| Chachuat, Benoit | Imperial Coll. London |

This paper presents a multi-physics modeling methodology for the quantitative prediction of microalgae productivity in raceway ponds by combining a semi-mechanistic model of microalgae growth describing photoregulation, photoinhibition and photoacclimation, with models of imperfect mixing based on Lagrangian particle-tracking and heterogeneous light distribution. The photosynthetic processes of photoproduction, photoregulation and photoinhibition are represented by a model of chlorophyll fluorescence developed by Nikolaou et al. (2015), which is extended to encompass photoacclimation. The flow is simulated with the commercial CFD package ANSYS, whereas light attenuation is described by the Beer-Lambert law as a first approximation. Full-scale simulation results are presented on extended time horizons. Comparisons are made in terms of areal productivities under both imperfect and idealized (CSTR) mixing conditions, and for various extraction rates and water depths.

| 16:20-16:40 | TuA2.4 |

*Metabolic Modeling of C. Sorokiniana Diauxic Heterotrophic Growth*

| Baroukh, Caroline | INRIA |
| Bernard, Olivier | INRIA |

Microalgae are promising microorganisms for the production of numerous molecules of interest, such as pigments, proteins or triglycerides that can be turned into biofuels. Heterotrophic growth on wastes represents an interesting approach to achieve higher biomass concentrations, while reducing cost and improving the environmental footprint. Wastes generally consist of a mixt of diverse molecules. It is crucial to understand microalgal metabolism in such conditions, where switching between substrates might occur. Metabolic modeling has proven to be an efficient tool for understanding metabolism and guiding the optimization of biomass or target molecule production. Here, we focused on the metabolism of *Chlorella sorokiniana* growing heterotrophically on acetate and butyrate. The metabolism was represented by 163 metabolic reactions. The DRUM modeling framework, with a mildly relaxed quasi-steady-state assumption,

was used to account for possible intracellular accumulation during switching between substrates. Six experiments were used to calibrate the model and eight experiments for the validation. The model efficiently predicted the experimental data, including the transient behavior. To the best of our knowledge, this is the first study to describe the dynamic metabolic fluxes of microalgae during heterotrophic and diauxic growth. It shows that an accurate model of metabolism can now be constructed, even in dynamic conditions, with the presence of several carbon substrates. It also opens new perspectives for the heterotrophic use of microalgae, especially for biofuel production from wastes.

| 16:40-17:00 | TuA2.5 |

*Metabolic Fluxes in Recombinant Streptomyces Lividans Analyzed with 13C-Based Metabolic Flux Analysis*

| Bouvin, Jeroen | KU Leuven |
| Daniels, Wouter | KU Leuven |
| Anné, Jozef | KU Leuven |
| Nicolai, Bart | KU Leuven |
| Bernaerts, Kristel | KU Leuven |

*Streptomyces lividans* is an interesting host for the production of heterologous proteins. Expression of these foreign proteins often results in a metabolic burden leading to unsatisfactory yields. In this work, metabolic fluxes in *Streptomyces lividans* producing thermostable cellulase A are quantified. More insight in metabolic changes is acquired by estimating the fluxes in the central carbon metabolism by means of stationary 13C-based metabolic flux analysis. Labelling was measured in proteinogenic amino acids, which were obtained from batch experiments with an optimally chosen mixture of uniformly labelled glucose and position one labelled glucose. The cellulase A producing strain shows an increased secretion of organic acids, while growth is less efficient. Intracellularly, an increase through the pentose phosphate pathway and the citric acid cycle is observed, which alters the redox potential. Production of NADH and NADPH is higher in the CelA-producing strain, although the need is expected to be lower.

# Program and Abstracts Wednesday October 12

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|---|---|
| 08:30-09:15 WePMP, Nave, **Plenary Diego di Bernardo** | |
| 09:15-09:45 WeKMP, Nave, **Keynote Birgit Schöberl** | |
| 09:45-10:20 WeCMP, Nave, **Coffee Break** | |
| 10:20-11:40 WeM1,    Nave, **Systems Medicine** | |
| 11:40-12:10 WeKAP, Nave, **Keynote Edda Klipp** | |
| 12:10-12:30 WeClP,   Nave, **Closing** | |

| **WePMP** | Nave |
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| **Diego di Bernardo** (Plenary Session) | |
| Chair: Bullinger, Eric | Otto-Von-Guericke Univ. Magdeburg |

| 08:30-09:15 | WePMP.1 |
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*Controlling Gene Expression from Inducible Promoters in Yeast and Mammalian Cells*

| di Bernardo, Diego | TIGEM |
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A crucial feature of biological systems is their ability to maintain homeostasis in spite of ever-changing conditions. In this talk, I will show how the engineering feedback control paradigm can be applied in synthetic biology in order to force a the expression of a gene to be in a desired range, or to change in time with a desired dynamics (e.g. pulsatile expression, sinusoidal expression etc.) from inducible promoters. Examples on the control of gene expression in yeast and mammalian cells will be shown.

| **WeKMP** | Nave |
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| **Birgit Schöberl** (Keynote Session) | |
| Chair: Findeisen, Rolf | OvG Univ. Magdeburg |

| 09:15-09:45 | WeKMP.1 |
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*From Systems Biology to Systems Medicine*

| Schöberl, Birgit | Merrimack |
|---|---|

Cancer is a complex disease and pathway redundancy often leads to resistance to targeted inhibitors. Here, we describe the comprehensive analysis of phenotypic and signaling responses of a panel of colorectal cancer cell lines to a single growth factor as well as the pairwise combination of growth factor treatments in the presence and absence of signaling inhibitors. These signaling inhibitors are the investigational agents MM-121 (anti-ErbB3 mAb), MM-141 (bispecific antibody targeting IGF1R and ErbB3) and MM-151 (olgioclonal mixture of anti-EGFR mAbs) from Merrimack's pipeline and were originally designed using Systems Biology insights into the pathways these agents are targeting. The results presented here demonstrate the use of phenotypic screening and computational modeling to reveal unexpected behaviors, identify positive and as well as negative biomarkers, and guide novel treatment strategies. The insights derived from our preclinical research resulted in the design of Merrimack's first Phase 1 basket clinical study. Patients will receive Merrimack's oligoclonal EGFR inhibitor, MM-151, in combination with another agent, either MM-121, MM-141 or trametinib. Each combination is intended to target a specific mechanism of resistance to EGFR inhibition and cover the most prevalent mechanisms of resistance. We will discuss how Systems Biology insights defined the assignment to one of the four arms of the clinical trial.

| **WeM1** | Nave |
|---|---|
| **Systems Medicine** (Regular Session) | |
| Chair: Raue, Andreas | Univ. of Freiburg |
| Co-Chair: Balsa-Canto, Eva | CSIC |

| 10:20-10:40 | WeM1.1 |
|---|---|

*Optimum Experimental Design for Patient Specific Mathematical Leukopenia Models*

| Jost, Felix | OvG Univ. Magdeburg |
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| Rinke, Kristine | OvG Univ. Magdeburg |
| Fischer, Thomas | OvG Univ. Hospital Magdeburg |
| Schalk, Enrico | OvG Univ. Hospital Magdeburg |
| Sager, Sebastian | OvG Univ. Magdeburg |

Mathematical models are essential for simulation-driven decision support for clinical doctors. For an estimation of parameters for patient specific models, values such as the number of certain blood cells need to be measured. In this paper we focus on leukopenia, a clinically important side effect arising from the treatment of leukemia with chemotherapy. A mathematical leukopenia model is presented describing the dynamics of leukocytes and we show that the standard deviations of the parameter estimates depend strongly on the timing of the measurements. We discuss the issue of measurement time points for two patients being in the consolidation phase of acute myeloid leukemia and provide optimal solutions. Optimized measurement time points and the thus enabled accurate simulations have a large impact: drug treatments can be adapted individually and patients may safely leave the hospital for longer and more convenient time intervals. The dynamics of leukocytes are modeled by a system of ordinary differential equations and the chemotherapy with cytarabine is described by a pharmacokinetics/pharmacodynamics model consisting of two compartments and a log-linear function representing the drug effect. The measurement time points are optimized by optimal experimental design. With optimal experimental design an average parameter uncertainty reduction of 57% (Patient 1) and 80% (Patient 2) can be achieved compared to the clinical experimental designs, with the same total number of measurements. These encouraging results motivate further research and an extension of the data basis to more patients.

| 10:40-11:00 | WeM1.2 |
|---|---|

*Modelling the Dynamics of Liver Renewal During Homeostasis and Regeneration*

| Cook, Daniel | Univ. of Delaware |
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| Ogunnaike, Babatunde A. | Univ. of Delaware |
| Vadigepalli, Rajanikanth | Thomas Jefferson Univ |

The liver is unique among mammalian organs because it has the potential to replace lost mass through homeostatic renewal or through a program of regeneration in response to tissue damage (up to 70-80% of lost mass). Several questions remain outstanding in the field of liver research: What are the network structures and kinetics that enable renewal and regeneration? How does the system dynamically operate to allow for both renewal paradigms? How could chronic diseases impair the renewal mechanisms? We pursued a computational modelling approach to explore the answers to these questions.

| 11:00-11:20 | WeM1.3 |
|---|---|

*Mathematical Modelling the Decision Making of Lung Epithelial Cells under Infection*

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| Santos Rosales, Guido | FAU Univ. Nürnberg-Erlangen |
| Lai, Xin | Erlangen Univ. Hospital |
| Vera-Gonzalez, Julio | Univ. Erlangen |

Pneumonia is a common disease with high transmission rate and potentially dangerous. The disease is driven by an acute inflammatory response of the immune system against the pathogen. The final outcome initially depends on the signals trigger by local innate immune cells and epithelial cells in response to the pathogen. The epithelial cells of the lung act not only as passive barrier against the pathogen, but they are also able to activate the migration of immune cells and releasing cytokines which produce the inflammatory response. Activation of epithelial cell internal signaling pathways by the pathogen can give many different outputs, from inflammatory response, cell growth, cell death activation and releasing the tight junctions between cells, this last response produced by specific signals for barrier dysfunction. All the signaling pathways are integrated into a mathematical model based in ordinary differential equations so the final response of the cell could be predicted depending on the kind and intensity of the input, coming from the pathogen or from other local immune cells as macrophages, as well as the neighbor epithelial cells.

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| 11:20-11:40 | WeM1.4 |

*Inferring Causal Gene Targets from Time Course Expression Data*

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| Noh, Heeju | ETH Zurich, Swiss Inst. of Bioinformatics |
| Hua, Ziyi | ETH Zurich |
| Gunawan, Rudiyanto | ETH Zurich, Swiss Inst. of Bioinformatics |

In this work, we proposed a network analysis method called DeltaNeTS for inferring genetic perturbations from temporal transcriptional expression profiles. While several efficacious and robust network analysis methods exist for steady state data, a direct application of these methods to analyze time series expression data often leads to a poor prediction performance. DeltaNeTS is an extension of our previous method DeltaNet, which involves a single-step inference of gene regulatory network and gene targets from transcriptional profiles. In order to prevent reversals in the causal directions of gene regulations when analyzing time series data, DeltaNeTS employs an additional constraint based on the time derivatives of the temporal expression profiles. We demonstrated the advantages of DeltaNeTS over DeltaNet and a network analysis method called Time Series Network Inference (TSNI), by analyzing time-series expression data from in silico simulations and from microarray assays of *Saccharomyces cerevisiae* (yeast) and cultured human airway epithelial cells.

| **WeKAP** | Nave |
|---|---|
| **Edda Klipp** (Keynote Session) | |
| Chair: Gunawan, Rudiyanto | ETH Zürich |

| | |
|---|---|
| 11:40-12:10 | WeKAP.1 |

*Yeast Mating in Space and Time*

| | |
|---|---|
| Klipp, Edda | Humboldt-Univ. Zu Berlin |

Baker's yeast (Saccharomyces cerevisiae) has a diploid life-style, but under stress conditions it forms spores which then release haploid cells of mating types MATa and MATα. MATa cells are a frequently used model organism for many cell biological studies of cell cycle, metabolism or signaling. MATa and MATα cells can also mate to form diploid cells again. To this end they secrete the pheromones a-factor and α-factor, sense the opposite pheromone and form protrusions in the direction of a potential mating partner. Importantly, they cannot move towards their mating partner, thus the formation of the mating shape called shmoo is a significant investment. Combining experimental studies of the cellular responses to mating factor and the resulting shape changes with spatial mathematical modeling, we investigated three major steps in the mating process. Specifically, we asked (i) how yeast cells communicate to form sharp gradients allowing precise decisions, (ii) how the individual cells sense the resulting gradients and (iii) how they translate the sensed information into shape changes.

# Author Index

# Keyword Index

## Venue Map Johanniskirche

# Program at a Glance

**Sunday October 9**

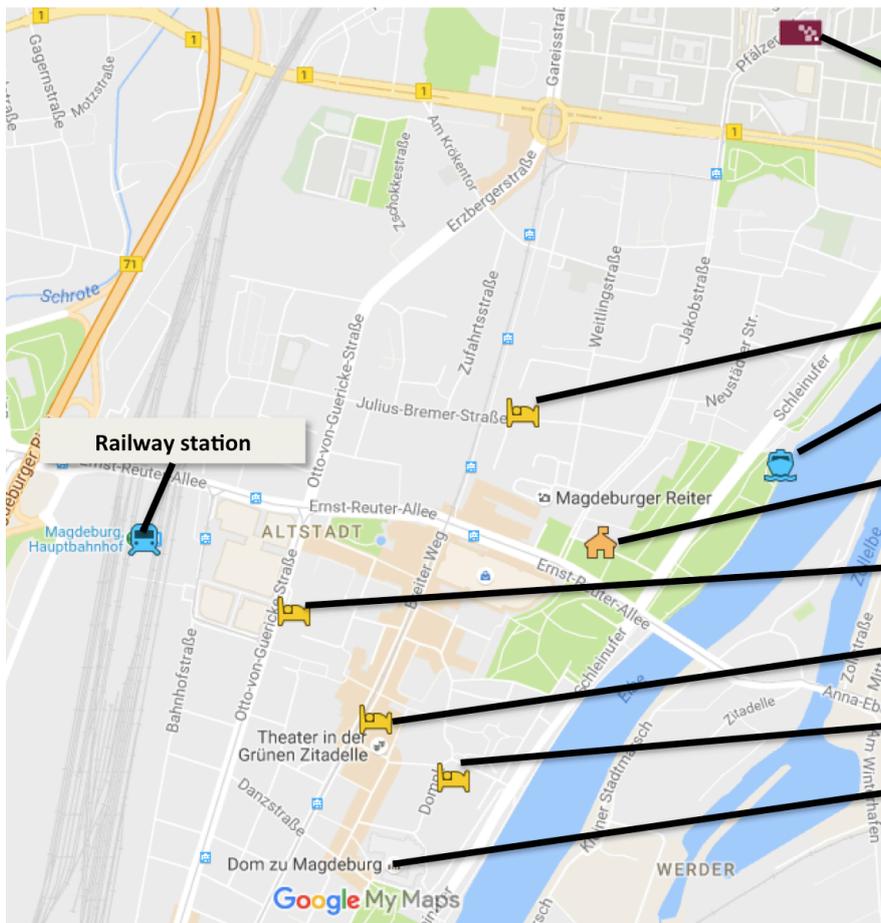| | |
|---|---|
| 13:30-17:00 SuW1, G28 room 026 **Workshop: Optimization in Systems and Synthetic Biology: Concepts, Methods and Illustrative Examples** | 13:30-17:00 SuW2, G28 room 027 **Workshop: Kinetic and Optimization Based Models for Understanding the Regulation of Cellular Metabolism** |
| 18:00-20:00 SuRP, G28, **Welcome Reception** | |

**Monday October 10**

| | |
|---|---|
| 08:30-08:45 MoOP.   Nave, **Opening** | |
| 08:45-09:30 MoPMP, Nave, **Plenary Guy-Bart Stan** | |
| 09:30-10:00 MoKMP, Nave, **Keynote Robert S. Parker** | |
| 10:00-10:30 MoCMP, Nave, **Coffee Break** | |
| 10:30-12:10 MoM1,   Nave, **Synthetic Biology** | 10:30-12:10 MoM2, Gallery **Modelling – Health** |
| 12:10-14:10 MoPP,   Nave, **Poster Session I with Lunch** | |
| 14:10-15:00 MoPAP, Nave, **Public Plenary Frank Doyle** | |
| 15:10-15:40 MoKAP, Nave, **Keynote Rudi Gunawan** | |
| 15:40-16:10 MoCAP, Nave, **Coffee Break MA** | |
| 16:10-17:50 MoA1,   Nave **Modelling–Microbial Systems** | 16:10-17:50 MoA2, Gallery **Methods** |
| 17:50-19:30 MoCP, **Guided city walk and visit of the Magdeburg Cathedral** | |

**Tuesday October 11**

| | |
|---|---|
| 08:30-09:15 TuPMP, Nave, **Plenary Hans Westerhoff** | |
| 09:15-09:45 TuKMP, Nave, **Keynote Bas Teusink** | |
| 09:45-10:20 TuCMP, Nave, **Coffee Break TM** | |
| 10:20-12:00 TuM1, Nave **Dynamics and Control** | 10:20-12:00 TuM2, Gallery **Optimization Based Methods for Understanding the Regulation of Cellular Metabolism** |
| 12:00-14:00 TuPP,   TM, **Poster Session II with Lunch** | |
| 14:00-14:30 TuKA1P, Nave, **Keynote Pablo Iglesias** | |
| 14:30-15:00 TuKA2P, Nave, **Keynote Jörg Stelling** | |
| 15:00-15:20 TuCAP,   Nave, **Coffee Break** | |
| 15:20-17:00 TuA1, Nave **Session in Memoriam of Peter Wellstead** | 15:20-17:00 TuA2, Gallery **Biotechnology Methods & Applications** |
| 17:30-23:00 TuRP, **Conference Banquet and Boat Tour** | |

**Wednesday October 12**

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|---|
| 08:30-09:15 WePMP, Nave, **Plenary Diego di Bernardo** |
| 09:15-09:45 WeKMP, Nave, **Keynote Birgit Schöberl** |
| 09:45-10:20 WeCMP, Nave, **Coffee Break** |
| 10:20-11:40 WeM1,   Nave, **Systems Medicine** |
| 11:40-12:10 WeKAP, Nave, **Keynote Edda Klipp** |
| 12:10-12:30 WeClP,   Nave, **Closing** |

Welcome Reception
Pfälzerplatz
Building 28, OvGU

Hotel Ratswaage

Departure Ship cruise

Conference venue
Johanniskirche
Johannisbergstrasse 1

Maritim Hotel

Hundertwasser
building

Motel One

Cathedral

Banquet
Herrenkrug
Hotel

Railway station