International Federation of Automatic Control
in cooperation with the CACHE Corporation

Program Booklet

FOSBE 2019

8th IFAC Conference on Foundations of Systems Biology in Engineering

Edited by
Jesús Picó, Universitat Politècnica de València, Spain
Eva Balsa-Canto, IIM-CSIC, Spain
Steffen Waldherr, KU Leuven
Julio R Banga, IIM-CSIC, Spain
## Program at a Glance

### Tuesday October 15, 2019

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<td>15:00-18:30</td>
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<td><strong>Opening Ceremony</strong></td>
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<td>08:30-09:00</td>
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<tr>
<td>Auditorio Cubo Azul (Blue Cube’s Auditorium)</td>
<td><strong>Computational Methods for Large-Scale Dynamic Modelling in Systems Medicine</strong></td>
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<tr>
<td><strong>A Single Biomolecular Controller Topology Achieves Robust Perfect Adaptation for Arbitrary Intracellular Networks with Noisy Dynamics. Mustafa Khammash, Dept. of Biosystems Science &amp; Engineering, ETH Zurich</strong></td>
<td>10:00-10:30</td>
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<td>Auditorio Cubo Azul (Blue Cube’s Auditorium)</td>
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<tr>
<td>Auditorio Cubo Azul (Blue Cube’s Auditorium)</td>
<td><strong>Dynamics and Control of Biological Systems I</strong></td>
</tr>
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<td><strong>Computational Design of Biomolecular Circuits</strong></td>
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<tr>
<td>Auditorio Cubo Azul (Blue Cube’s Auditorium)</td>
<td><strong>Dynamics and Control of Biological Systems II</strong></td>
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<tr>
<td><strong>Design and Control of Synthetic Biological Systems and Circuits</strong></td>
<td>16:00-17:00</td>
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<tr>
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<tr>
<td><strong>Keynote 1. Modelling for Systems Medicine. Neda Bagheri, McCormick School of Eng. &amp; Applied Science, Northwestern University</strong></td>
<td>17:00-17:45</td>
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<tr>
<td>Auditorio Cubo Azul (Blue Cube’s Auditorium)</td>
<td><strong>Keynote 2. Never Lost in Translation: How Systems Pharmacology Can Bridge from Early Research to Proof-Of-Concept in Humans. Stephan Schaller, Founder and CEO, esqLABS GmbH</strong></td>
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<td>17:00-17:45</td>
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<td><strong>Conference Dinner</strong></td>
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10:00-10:30: WeBrMoC, Hall Cubo Azul (Blue Cube’s Hall), Coffee Break We

12:30-14:00: WeNLu, Hall Cubo Azul (Blue Cube’s Hall), Lunch We

14:00-16:00: WeAf1T1

**Auditorio Cubo Azul (Blue Cube’s Auditorium)**

14:00-16:00: WeAf1T2

**Auditorio Cubo Azul (Blue Cube’s Auditorium)**

### Thursday October 17, 2019

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<td><strong>Computational Modelling of Whole-Body Metabolism Permits Novel Insight into Host-Microbiome Co-Metabolism. Ines Thiele, National University of Ireland, Galway</strong></td>
<td><strong>Modelling of Complex Biological Systems I</strong></td>
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<td>09:00-10:00</td>
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<td>Auditorio Cubo Azul (Blue Cube’s Auditorium)</td>
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<td>10:00-10:30</td>
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<tr>
<td>Auditorio Cubo Azul (Blue Cube’s Auditorium)</td>
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<tr>
<td><strong>09:00-09:45 FrMo1P</strong>&lt;br&gt;Auditorio Cubo Azul (Blue Cube’s Auditorium)&lt;br&gt;<strong>Keynote 3. Understanding Biological Function in the Context of Biological Heterogeneity. Alexander Hoffmann, Institute for Quantitative and Computational Biosciences, UCLA</strong></td>
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<tr>
<td><strong>09:45-10:15 FrBrMoC, Hall Cubo Azul (Blue Cube’s Hall), Coffee Break Fr</strong></td>
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<td><strong>10:15-11:51 FrMo2T1</strong>&lt;br&gt;Auditorio Cubo Azul (Blue Cube’s Auditorium)&lt;br&gt;<strong>Network Inference and Modelling</strong></td>
<td><strong>10:15-11:51 FrMo2T2</strong>&lt;br&gt;Salón de Actos Cubo Rojo (Red Cube’s Events Room)&lt;br&gt;<strong>Control and Optimisation of Microalgae</strong></td>
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<tr>
<td><strong>12:00-13:00 FrNP</strong>&lt;br&gt;Auditorio Cubo Azul (Blue Cube’s Auditorium)&lt;br&gt;<strong>Keynote 4. Small Multicellular Cohorts Are Engineered to Function As a Distributed Detector of Rare Multivariate Events. Daniel Georgiev, Founder and CEO, XENO Cell Innovations S.r.o</strong></td>
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<td><strong>13:00-14:00 FrAfCo, Hall Cubo Azul (Blue Cube’s Hall)</strong>&lt;br&gt;<strong>Farewell Cocktail</strong></td>
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Welcome Message

It is our pleasure to welcome you to the 8th IFAC Conference on Foundations of Systems Biology in Engineering (FOSBE2019) in Valencia, Spain 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 modelling to systems medicine.

FOSBE2019 features a varied scientific program, including plenary and invited keynote presentations, contributed and invited technical sessions, three pre-conference workshops, and a social program that will take you to the cultural and natural sites of the city of Valencia. The technical sessions are hosted in the Polytechnic City of Innovation (CPI) building located at the campus of the Universitat Politècnica de València (UPV).

Based on a strict reviewing process, the International Program Committee selected 48 contributions for oral presentation and 17 for poster one. The program consists of six regular sessions and four invited ones, two poster sessions, two plenary talks and four invited keynote ones, two of them from industry. Each day begins and ends with a plenary talk and or a keynote. The program is complemented by three interesting pre-conference workshops that take place on Tuesday, October 15.

The social program consists of the opening reception on Tuesday evening in the Blue Cube’s Hall (Hall del Cubo Azul) in the CPI building of the UPV University and the Conference Banquet on Thursday evening preceded by a boat tour on the Albufera Lake, one of Valencia’s natural treasures.

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 city of Valencia, one of the most important ones in the Mediterranean coast during the fourteenth and fifteenth centuries. You can enjoy the gothic buildings in the old town, the modern buildings in the City of Arts and Science located in the old river bed, the evening-night atmosphere of the El Carme old quarter, taste a good and famous paella at the beach, etc. 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 Valencia.

Best regards,

Jesús Picó (NOC chair), on behalf of the NOC

Steffen Waldherr (IPC chair), on behalf of the IPC
Committees

National Organizing Committee (NOC)

Chair: Prof. Jesús Picó. Universitat Politècnica de València
Co-chair: Dr. Eva Balsa-Canto. National Spanish Research Council
Co-chair: Dr. José Luis García. I2SysBio, National Spanish Research Council
Vice-chair from industry: Dr. Daniel Ramon-Vidal. Biopolis S.L. – ADM

NOC members
José Luis Navarro Fernando N. Santos-Navarro Alejandro Villaverde
Alejandro Vignoni Yadira Boada
Enric Picó-Marco Irene Otero-Muras

International Program Committee (IPC)

Chair: Prof. Dr. Steffen Waldherr. KU Leuven
Co-chair: Dr. Julio R. Banga. National Spanish Research Council
Vice-chair from industry: Isabel Rocha. Pro-Rector NOVA University Lisbon & Chief Scientific Officer, SilicoLife Lda

IPC Conference Program Editors
Julio R. Banga, Juergen Hahn, Diego A. Oyarzún, Steffen Waldherr, Jan Hasenauer, Eva Balsa-Canto, Rudi Gunawan, Jesús Picó.

IPC Members
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Philippe Bogaerts BE Gabor Szederkenyi HU
Hector Budman CA Diego di Bernardo IT
Radhakrishnan Mahadevan CA Yutaka Hori JP
Brian Ingalls CA Kwang-Hyun Cho KR
Jörg Stelling CH Alejandro Vargas MX
Mustafa Khammash CH Giulia Giordano NL
Chuanhou Gao CN Nadav Bar NO
Steffen Klmet DE Eugenio Ferreira PT
Olaf Worikenhauer DE Filippo Menolascina UK
Jan Hasenauer DE Diego Oyarzún UK
Nicole Radde DE Guy-Bart Stan UK
Nikolaus Sonnenschein DE Angel Gofí UK
Julio Saez-Rodriguez DE Antonis Papachristodoulou UK
Frank Allgower DE Pablo Carbonell UK
Rolf Findeisen DE Visakan Khadirkamanathan UK
Jesús Picó ES Juergen Hahn US
Eva Balsa-Canto ES Pablo Iglesias US
Juli Peretó ES Rudi Gunawan US
Javier Macía ES Michael Henson US
Olivier Bernard FR Hana El-Samad US
Hidde de Jong FR Jennifer Reed US
Madalena Chaves FR
Anne Goelzer FR
Jean-Loup Faulon FR
Sponsors

Main sponsoring committee:
- Technical Committee 8.4 Biosystems and Bioprocesses

Co-sponsoring committees:
- TC 2.3 Non-linear Control Systems
- TC 2.5 Robust Control
- TC 6.1 Chemical Process Control
- TC 8.1 Control in Agriculture
- TC 8.2 Biological and Medical Systems
- TC 8.3 Modelling and Control of Environmental Systems

Universitat Politècnica de València

The CACHE Corporation

Escola Tècnica Superior d’Enginyers Industrials de València (ETSII)

Institute for Automatic Control and Industrial Computing, ai2-UPV

Department of Systems Engineering and Control, DISA-UPV

Synthetic Biology and Biosystems Control Lab, SB²CLab-UPV

Processes, MDPI – Open Access Publishing
Registration, Social Program, Pre-Conference Workshops, Announcements

Registration Tuesday October 15 – Friday October 18

Tuesday 15, 14:00 – 19:30
Wednesday 16 – Thursday 17, 8:30 – 18:00
Friday 18, 8:30 – 12:00

The registration desk is located in the Blue Cube’s Hall, CPI building, UPV campus (building 8B) where the welcome reception will take place. See the map at the end of the brochure.

Welcome Reception Tuesday October 15, 18:30 – 20:00

The welcome reception will take place in the Blue Cube’s Hall of the CPI building (UPV). See the map at the end of the brochure. Complimentary drinks and food are provided.

Conference banquet and boat tour Thursday October 17, 18:30 – 23:00

The conference banquet will take place in the restaurant Nou Racó located in the Albufera Lake, a natural park 16 Km south of the UPV campus. It will be preceded by a boat trip on the lake at 19:00. The sunset will take place around 19:20. The busses will leave at 18:20 from the campus meeting point number 8 located in the Naranjos Avenue close to the CPI building. See the map at the end of the brochure. After the banquet, we will return to València in the same busses.

Please, report any dietary requirements as soon as possible

Pre-Conference Workshops

Three workshops are organized before the conference. They require specific registration. Late registration will be available on Tuesday 15 at 14:00 at the conference registration desk.

<table>
<thead>
<tr>
<th>Title</th>
<th>Contributors</th>
<th>Schedule</th>
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<tr>
<td>Analyzing and redesigning metabolic networks with CellNetAnalyzer</td>
<td>Philipp Schneider and Steffen Klamt</td>
<td>15:00 – 18:30</td>
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<tr>
<td>Multi-omics data and multiscale modelling in winemaking</td>
<td>Amparo Querol, Eladio Barrio and Eva Balsa-Canto</td>
<td>15:00 – 18:30</td>
</tr>
<tr>
<td>Standarization for Synthetic Biology</td>
<td>Alejandro Vignoni, Angel Goñi and Diego Orzáez</td>
<td>15:00 – 18:30</td>
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</table>

Find the detailed program of each workshop at http://fosbe2019.ai2.upv.es/workshops/. The workshops take place in parallel sessions in the rooms Aprende, Debate and Descubre in the Cubo Rojo (Red Cube). See the map at the end of the brochure.

Wireless Network

Wireless network is provided throughout the campus via Eduroam. Temporal access to wifi network will also be provided, user and password will be given at registration.
Instruction for Presenters, Session Chairs, Posters

Oral Presentations

The allocated time for the talks are as follows:

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<tr>
<th>Type</th>
<th>Presentation time</th>
<th>Discussion time</th>
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</thead>
<tbody>
<tr>
<td>Plenary</td>
<td>50 minutes</td>
<td>6 minutes</td>
</tr>
<tr>
<td>Keynote</td>
<td>40 minutes</td>
<td>5 minutes</td>
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<tr>
<td>Regular</td>
<td>20 minutes</td>
<td>4 minutes</td>
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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.

Best Student Paper Award: an award for the best paper presented by a student will be given during the closing session, consisting of a certificate and refunding of the conference fee.

Poster Presentations

The poster sessions take place in the Hall of the Blue Cube (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.

Best Student Poster Award: an award for the best poster presented by a student will be given during the closing session, consisting of a certificate and refunding of half the conference fee.

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 above for details. Remind the authors at the 3-minute mark (e.g., at the 17th 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

A single biomolecular controller topology achieves Robust Perfect Adaptation for arbitrary intracellular networks with noisy dynamics.

Mustafa Khammash
Dept. of Biosystems Science & Engineering
ETH Zurich

Abstract: Homeostasis is a recurring theme across living systems. Homeostatic mechanisms frequently ensure that regulated variables robustly and fully adapt to environmental perturbations. This robust perfect adaptation (RPA) feature is achieved by incorporating mathematical integration in a negative feedback strategy. Despite its benefits in natural circuits, the synthetic realization of integral feedback has remained elusive due to the complexity of the required biological computations. In this talk, I will show that there is fundamentally a single biomolecular controller topology that realizes integral feedback for arbitrary intracellular networks with noisy dynamics. Such a controller ensures robust perfect adaptation for the cell population-average as well as for the time-average of single cells. I will then present the first synthetic gene network implementation of such an integral controller in a living cell, and demonstrate its tunability and adaptation properties. Finally, I will highlight the genetic controller’s versatility by discussing its application to population growth control.

Computational modelling of whole-body metabolism permits novel insight into host-microbiome co-metabolism.

Ines Thielean
School of Medicine
National University of Ireland, Galway

Abstract: Precision medicine relies on the availability of realistic, mechanistic models that capture the complexity of the human body. Comprehensive computational models of human metabolism have been assembled by the systems biology community, which summarize known metabolic processes occurring in at least one human cell or organ. However, these models have not yet been expanded to connect with whole-body level processes. To address this shortcoming, we built whole-body metabolic models of a male (deemed Harvey) and a female (deemed Harvetta) starting from the existing human metabolic models, physiological and anatomic information, comprehensive proteomic and metabolomic data, as well as biochemical data obtained from an extensive manual literature review. We tested the predictive capabilities of the resulting whole-body metabolic models against the current knowledge of organ-specific and inter-organ metabolism. The final models contain 28 organs. Importantly, these whole-body models can be expanded to include the strain-resolved metabolic models of gut microbes. By parameterizing the whole-body metabolic models with physiological and metabolomic data, we connected physiology with molecular-level processes through networks of genes, proteins, and biochemical reactions. As a sample application of the whole-body metabolic models, I will demonstrate how different microbial composition leads to differences in host metabolism, such as the capability to produce important neurotransmitters in the brain and flux through liver enzymes, with implications for the gut-brain axis as well as for microbiome-mediated liver toxicity. The predictions were consistent with our current understanding but also highlighted that different microbiota composition can lead to high inter-person variability. I envisage the microbiome-associated whole-body metabolic models will usher in a new era for research into causal host-microbiome relationships and greatly accelerate the development of targeted dietary and microbial intervention strategies.
Invited Keynote talks

Modelling for systems medicine.

Neda Bagheri
Department of Biology and Chemical Engineering,
University of Washington, USA

Abstract: Computational models are essential tools that can be used to simultaneously explain and guide both biological and medical intuition. With increasingly high-resolution, high-throughput, and dynamic experimental data, computational biologists are better equipped to develop informed models that aim to characterize complex cellular responses and direct experimental design. My lab operates at this evolving interface between chemical engineering and biology; we employ machine learning, dynamical systems, and agent-based modelling strategies to help explain biological observations, and to elucidate design principles that drive both individual cellular decisions and cell populations. We are interested in the inherent multiscale nature of cells—how “the whole is greater than the sum of its parts”—and in predicting cell population dynamics from the composition of simpler biological modules to advance medicine.

Never lost in translation: How systems pharmacology can bridge from early research to proof-of-concept in humans.

Stephan Schaller
Founder and CEO, esqLABS GmbH

Abstract: Quantitative, population-based simulations of clinical trials are usually conducted at later stages of drug development typically requiring clinical (human) data from Phase I/II/IIb of drug development. We have developed a digital platform, the Diabetes Platform within the OSP Suite (www.open-systems-pharmacology.com), for early prediction of clinical (trial) outcomes by leveraging physiological and systems-biology knowledge to translate early in-vitro and preclinical outcomes to the clinic. The Diabetes Platform applies a modular concept to allow efficient, flexible, and transparent multi-scale quantitative systems pharmacology (QSP) modelling and simulation. The software allows to combine cons of physiologically-based (PB) pharmacokinetic (PK) models (i.e. absorption, distribution, metabolization and excretion) of small and large molecules in different animal species and human populations with cellular-level systems-biology concepts to describe pharmacodynamic (PD) effects to create a physiologically- and mechanism-based translational modelling & simulation platform. The Diabetes Platform integrates subcellular mechanisms, such as islet biology, insulin secretion and -receptor dynamics across different animal species and human diabetes types and has been validated on various test scenarios with different treatment options, e.g. multiple insulin types, glucagon, GLP-1 and GIP analogues and SGLT1/2 inhibitors. The platform achieved high accuracy in describing the PK/PD of glucose, and respective treatments on both, the quantitative and the qualitative level. In conclusion, characterization of both the animal and human glucose metabolism on a structural and mechanistic level is of great value when new treatments need to be analyzed and translated during transition from research to development. The captured structural and mechanistic knowledge allows informed extrapolations and thus accurate predictions of the treatment PK, the mode of action concept and the effect (PD) on whole-body glucose metabolism when translating from animals to humans. Leveraging its PBPK and QSP framework and a population of characterized in-silico diabetes patients, the platform allows population-level in-silico first-in-man and proof-of-concept evaluations for conceptualized treatments of diabetes. This can be done by translation of either pre-clinical outcome data or in-vitro compound properties at the drug discovery or lead-optimization stage.
Understanding biological function in the context of biological heterogeneity.

Alexander Hoffmann
Institute for Quantitative and Computational Biosciences
University of California, Los Angeles, USA

Abstract: Biological heterogeneity is a hallmark of biomedicine at any level, whether patients diagnosed with the same cancer but showing differential treatment success, fate decisions by genetically identical cells, or the signaling dynamics of immune cells responding to pathogens or cytokines. We have employed computational modelling of cellular responses and the underlying molecular network to understand the sources of biological heterogeneity and learn about biological function. Combining data-driven and knowledge-based modelling approaches has allowed us to quantify extrinsic and intrinsic noise sources, distinguish between static and dynamic network features that have predictive value and may function as prognostic biomarkers, and decipher the codewords of the language of immune sentinel cells. Overall, we find that biological function may emerge in different physiological contexts either because of or in spite of biological heterogeneity.

Small multicellular cohorts are engineered to function as a distributed detector of rare multivariate events.

Daniel Georgiev
Founder and CEO, XENO Cell Innovations

Abstract: Rare events, ipso facto, underlie early disease detection. Univariate rare events are standardly detected with highly specific molecular probes (e.g., antibodies or oligos). Routine detection of multivariate rare events is far more cumbersome. State-of-the-art solutions brute force the problem with high power instruments (e.g. flow cytometers or lab-on-chip devices). Not surprisingly, natural immune systems far outperform these solutions with distributed, hierarchical signal processing. The utility of these is however limited as the mechanisms remain concealed behind their biological complexity. This talk will present a solution currently being developed to product wherein microbial cohorts function as biocomputing units in detecting rare cells according to their multivariate surface profiles. Specific topics will include the lessons learned while addressing physical challenges inherent to multicellular signal processing within small cohorts of no more than one hundred individual cells. The ultimate hope of the talk is to use this commercially relevant case study to motivate benchmark problems in synthetic biology.
## Program Tuesday October 15

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<tr>
<td>Workshop 1: Analyzing and Redesigning Metabolic Networks with CellNetAnalyzer</td>
<td>Workshop 2: Multi-Omics Data and Multiscale Modelling in Winemaking</td>
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**18:30-20:00 TuAf2Wc, Hall Cubo Azul (Blue Cube's Hall)**

*Welcome Reception*
production of chemicals and materials in the new biofoundries faces the challenge of dealing with increasingly complex libraries of genetic circuits consisting of multiple gene variants from different sources and with different translational tuning, along with multiple promoter libraries, different vector copy number, resistance cassette, or host strain. In order to streamline the biomanufacturing pipeline, smart design rules are necessary to find the trade-offs between experimental design and predictive strain modeling for synthetic biology production of chemicals. Here, we explore the Pareto surface spanned by the optimal experimental design space of combinatorial libraries that are found in a large-scale diverse set of genetic circuits and plasmid vectors, and learning efficiency of their associated metabolic pathway dynamics. Engineering rules for metabolic pathway design are validated by these means, suggesting optimal synthetic biology design approaches for biomanufacturing pipelines.

**Technical Program for Wednesday October 16, 2019**

**WeMo2T1**
Computational Design of Biomolecular Circuits (Invited Session)

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<td>Oyarzún, Diego A. (University of Edinburgh)</td>
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<td>Otero-Muras, Irene (IIM-CSIC)</td>
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<td>11:42-12:06</td>
<td>WeMo2T1.4</td>
<td>Oyarzún, Diego A. (University of Edinburgh)</td>
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**Efficient Learning in Metabolic Pathway Designs through Optimal Assembling (I)**

**Leveraging Resource Competition for Part Characterization in Cell-Free Extracts (I)**
The rational design of complex biocircuits requires well-characterized genetic parts. Unfortunately, the behavior of these parts depends on their cellular context. One major source of context-dependence is competition for shared cellular resources, introducing coupling among virtually all components of a genetic circuit. By explicitly accounting for the scarcity of these resources, here we demonstrate how the resulting coupling phenomenon can be leveraged to characterize non-fluorescent parts by monitoring the expression of fluorescent probes. In particular, we develop a protocol that combines fluorescent measurements with mathematical modeling to extract information about the expression of non-fluorescent parts based on the loading on fluorescent probes due to competition effects. Furthermore, by quantifying the information content of candidate experiments, both experimental conditions and fluorescent probe parts can be optimized to minimize parameter uncertainty, thus leading to sharp parameter estimates. To validate our results, we demonstrate that the developed method can be successfully used for indirect parameter characterization considering in vitro data.

12:06-12:30 WeMo2T1.5

Bayesian Model Selection in Synthetic Biology: Factor Levels and Observation Functions (I), pp. 24-31

Bandiera, Lucia University of Edinburgh, School of Engineering, IBioE
Gomez Cabeza, David University of Edinburgh
Balsa-Canto, Eva CSIC
Menolascina, Filippo University of Edinburgh

Data-driven inference of the most plausible mechanistic model within a set of candidates is a major hurdle in synthetic and systems biology. Probabilistic model selection is hampered by limitations in the quality and amount of biological data. Furthermore, the computational cost of discriminating between competing models often leads the user to skip model selection and subjectively choose a model. To challenge this practice, here we took a genetic toggle switch built in E. coli, considered three alternative models of it and used a Bayesian approach to rank these models based on the evidence from in vivo data. As the ranking depends on the information content of the data, we use Bayesian optimisation to design maximally informative inputs, i.e. chemical stimuli for the cells. We then explore how the optimality of such stimuli depends on the degrees of freedom in the optimisation (i.e. the number of segments in the input), showing a decrease of the attainable discriminatory power with the dynamic properties of the perturbation. We finally investigate the effect that the observable(s) selected in the optimisation exerts on the outcome of the latter. Our results suggest that Bayesian optimisation-based experimental design can be adopted as a means to discriminate between competing models of a gene regulatory network.

10:54-11:18 WeMo2T2.2

Impact of Changing Cell-Cell Communication Network in Models of Epithelial Pattern Formation (I), pp. 38-44

Varela, Pedro Instituto Gulbenkian De Ciência
Monteiro, Pedro T. INESC-ID / IST - Universidade De Lisboa
Chauviya, Claudine Instituto Gulbenkian De Ciência

When modelling multi-cellular systems, one has to account for cell-cell signalling in addition to the molecular networks driving cell behaviours. Here, we aim at exploring how the topology of the cell-cell communication network impacts the behaviour of the whole multi-cellular system. More precisely, we focus on epithelial pattern formation, on which our question can be rephrased in terms of cell sizes and shapes. Relying on a logical modelling framework, and using a simple lateral inhibition model over a population of epithelial cells, we assess the model behaviours considering a variety of communication networks. This study suggests that reasonable deviations from a fixed grid (with regular hexagonal shaped cells) do not change much the resulting patterns. We further explore the impact of cell shapes and show that characteristics such as network regularity and number of shared neighbours of contacting cells are relevant to quality such deviations.

11:18-11:42 WeMo2T2.3

A Comparison of Methods for Quantifying Prediction Uncertainty in Systems Biology (I), pp. 45-51

Raimundez, Álvaro IIM-CSIC
Menolascina, Filippo University of Edinburgh, School of Engineering, IBioE
Hasenauer, Jan Technical University of Munich, Helmholtz Zentrum München
Banga, Julio R. IIM-CSIC (Spanish Council for Scientific Research)

The parameters of dynamical models of biological processes always possess some degree of uncertainty. This parameter uncertainty translates into an uncertainty of model predictions. The trajectories of unmeasured state variables are examples of such predictions. Quantifying the uncertainty associated with a given prediction is an important problem for model developers and users. However, the nonlinearity and complexity of most dynamical models renders it nontrivial. Here, we evaluate three state-of-the-art approaches for prediction uncertainty quantification using two models of different sizes and computational complexities. We discuss the trade-offs between applicability and statistical interpretability of the different methods, and provide guidelines for their application.

11:42-12:06 WeMo2T2.4

Literature and Data-Driven Based Inference of Signalling Interactions Using Time-Course Data (I), pp. 52-57

Gjerga, Enio RWTH Aachen
Trairaphisan, Panuwat University Hospital Heidelberg
Gabor, Attila MTA SZTAKI
Cellular activity and responses to stimuli are governed through an elaborated communication process called cell signalling. The modelling of signalling mechanisms has the potential to help us understand the regulatory processes determining cellular behaviour. One approach to derive models of signalling networks is from data alone. Another one is to use prior knowledge networks (PKNs) derived from literature or experts’ knowledge to build models that are trained to data. Both approaches have limitations. Data-driven methods can infer many false-positive interactions. Literature-constrained methods, on the other hand, are limited to model only known interactions. To overcome these limitations, within a logic ordinary differential equations (ODE) formalism, we have developed Dynamic-Feeder. The framework identifies and incorporates new possible links to the network and then it evaluates their effects based on how the models predict the data. Dynamic-Feeder combines data-driven inference methods with general literature-based knowledge of proteins interaction networks (PIN’s). We illustrate our method with a published case study using phosphoproteomic data upon perturbation of breast cancer cell lines.

In this talk we present how, thanks to its particular characteristics, the genetic toggle-switch can be used either to regulate the expression of two proteins of interest to some intermediate level [1-2] or as a bistable memory mechanism determining the future behavior of the host cell in multicellular applications [3].


Biological complex mechanisms with oscillatory behavior are often modeled by high dimensional nonlinear ODEs systems, which makes the analysis and understanding of the dynamics of the system difficult. In this work, we consider two reduced models that mimic the oscillatory dynamics of the cell cycle and the circadian clock, and study their coupling from a synthetic biology perspective. To improve the performance and robustness of the oscillatory dynamics in a living cellular environment, we consider the problem of augmenting the parameter region admitting periodic solutions. Moreover, we study the capacity for mutual period regulation and control of the coupling between the two reduced oscillators.

In order to survive, all living organisms need to process information from the environment and use signal integration to adapt their behaviour (Balazsi, van Oudenaarden and Collins, 2011). Imitation of these processes is essential for the further development of biotechnological and synthetic biology applications. Our previous work has described the implementation of a reference-comparator system within Escherichia coli, allowing cells to tune the expression of GFP by computing the difference between a quorum sensing molecule (AHL) and a chemical inducer (IPTG) (Annunziata et al., 2017). This was achieved by molecular-titration between orthogonal sigma factor and its cognate anti-sigma factor (Rhodius et al., 2013). In our previous work we performed batch experiments and showed, at steady state, that the comparator system is accurate and able to dynamically tune GFP expression in dependence of the two inducers, AHL and IPTG (Annunziata et al., 2017). We present here preliminary external feedback control results of the comparator system output while using IPTG as a control input. The experiments of the module characterisation validated in microfluidics was previously done in batch experiments. This provided useful time-lapses of its dynamics that can be instrumental for its use as the
“controller” cells in the multicellular control implementation described in Annunziata et al., (2017).

**Temperature-Dependent Dynamic Control of the TCA Cycle for Increased Volumetric Productivity of Itaconic Acid Production by Escherichia Coli**

Harder, Björn-Johannes  
Max Planck Institute for Dynamics of Complex Technical Systems

Bettenbrock, Katja  
Max Planck Institute for Dynamics of Complex Technical Systems

Klamt, Steffen  
Max Planck Institute for Dynamics of Complex Technical Systems

Introduction:  Itaconic acid is a high potential platform chemical which is currently industrially produced by Aspergillus terreus. We recently engineered E.coli (strain ita23) for growth-coupled synthesis of itaconic acid with high yield. Here we aimed to improve the productivity by applying a two-stage process strategy with decoupled production of biomass and itaconic acid.

Methods: Based on the design of the E. coli strain ita23 (Harder, Bettenbrock et al. 2016), we constructed a strain ita32, which, in contrast to ita23, has an active tricarboxylic acid (TCA) cycle. This enables the strain to grow with a fast growth rate of 0.52 h⁻¹ at 37°C, thus representing an ideal phenotype for the first stage, the growth phase. To down-regulate the TCA cycle and thus to switch from growth to itaconic acid production in the second stage, we replaced the promoter of the isocitrate dehydrogenase by the Lambda promoter (pL) in strain ita36A. The expression of this promoter was controlled by the temperature-sensitive repressor Cl857 which is active at lower temperatures (30°C). The respective strain ita36A grew with a fast growth rate at 37°C and switched to production of itaconic acid at 28°C.

Results: To study the impact of the process strategy on productivity we performed one-stage and two-stage bioreactor cultivations with strain ita36A. The two-stage process enabled fast formation of biomass resulting in improved peak productivity of 0.86 g itaconic acid/L/h (+48%) and volumetric productivity of 0.39 g itaconic acid/L/h (+22%) after 120 h in comparison to the one-stage process. With our dynamic production strain, we also resolved the glutamate auxotrophy of ita23 and increased the itaconic acid titer to 47 g/L.

Discussion: Here we selectively knocked-down an essential gene in E. coli to design a two-stage process for improved volumetric productivity. The control by temperature avoids excessive inducers and has the potential to be generally used to improve cell factory performance.

**Towards Automated Control of Embryonic Stem Cell Pluripotency**

Khazim, Mahmoud  
University of Bristol

Postiglione, Lorena  
TIGEM

Pedone, Elisa  
University of Bristol

Rocca, Dan  
University of Bristol

Zahra, Carine  
University of Bristol

Marucci, Lucia  
University of Bristol

Mouse embryonic stem cells (mESCs) have been shown to exist in three distinct pluripotent states (ground, naïve and primed pluripotent states), depending on culture conditions. External feedback control strategies have been so far, mainly used to automatically regulate gene expression in bacteria and yeast. Here, we exploit a microfluidics/microscopy platform and segmentation and external feedback control algorithms for the automatic regulation of pluripotency phenotypes in mESCs. We show feasibility of automatically controlling, in living mESCs, levels of an endogenous pluripotency gene, Rex1, through a fluorescent reporter, used as control output, and drugs commonly used to modulate pluripotency (i.e. MEK kinase and Gsk3β inhibitors) as control inputs. Our results will ultimately aid in the derivation of superior protocols for pluripotency maintenance and differentiation of mouse and human stem cells.

**Visual-Vestibular Compensation in Balance Recovery: A Function Transfer Model-Based Analysis**

Voda, Alina  
University Joseph Fourier Grenoble 1

Martin, Olivier  
GIPSA-Lab, CNRS Univ. Grenoble-Alpes

Naves Neto, Paulo  
GIPSA-Lab

Gascuel, Jean-Dominique  
LJK - CNRS Université Grenoble-Alpes

Schmerber, Sebastien  
Grenoble University Hospital, University Grenoble-Alpes

During immersive balance rehabilitation, automatic visual-vestibular compensations occur to reduce the patients’ visual reliance and improve the equilibrium. This paper describes the use of an identification procedure to characterise the relationship between visual stimulation features involved in this adaptive sensory compensation, and the balance improvement. The purpose is to determine the stimulus-response transfer functions (TF) associated to the equilibrium enhancement. Standing vestibular patients were stimulated by visual virtual flows, whose pattern and speed changed to the equilibrium enhancement. Standing vestibular patients were stimulated by visual virtual flows, whose pattern and speed changed throughout successive stimulation sessions. The analysis of the feet pressure, disequilibrium, and identified models parameters for one representative vestibular patient, showed that TF parameters evolved related to the gradual balance recovery boosted by the visual-vestibular compensation. This results suggest that identified TF parameters are suitable indicators for measuring the effect of sensory substitution on equilibrium recovery. This first step to model the relationship between the sensory re-weighting flexibility and the adaptation of postural commands is essential for future clinical studies using identification methods for sensorimotor evaluation in individualized vision-based balance rehabilitation.

Keywords: Human balance deficit, visual-vestibular compensation, virtual reality, rehabilitation, sensory integration, transfer function model, adaptive motor control, modelling.
Cells in a clonal cell-population exhibit a significant degree of cell-to-cell variability in their responses to an external stimulus. In order to model a heterogeneous intracellular process, the individual-based population model (IBPM) has been developed in the past. Specifically, the IPBM approach can represent the heterogeneous dynamics in a cell population with a system of differential equations, whose model parameters follow probability density functions (PDF) instead of being constants. Therefore, in order to accurately predict the heterogeneous cellular dynamics, it is important to infer the PDFs of the model parameters from available experimental measurements. In this study, we propose a methodology to estimate the PDFs of the model parameters from population snapshot measurements obtained from flow cytometry. First, the PDFs of the model parameters are assumed to be normal so that a finite dimensional vector will be inferred from the measurements instead of inferring PDFs, which are infinite dimensional. Second, the sensitivity analysis is performed to identify which PDFs of the model parameters are identifiable and should be estimated from the available measurements. Next, in order to reduce the excessive number of parameters of the IBPM during the PDF estimation process, an NNM is developed so that the output PDFs can be computed for given parameter PDFs. Lastly, the NNM is used to estimate the PDFs of the model parameters by minimizing the difference between the measured and predicted PDFs of the output. To show the effectiveness of the proposed methodology, the PDFs of parameters of a TNF signaling model were estimated from in silico measurements.

16:00-17:00 WeBrAfCP.2
Implementation of an On-Line Monitoring Technique in Industrial Bioethanol Fermentations, pp. 119-120
Soares, Matheus
GlobalYeast
Ribeiro, Vanessa
GlobalYeast
Richa, Rodrigo
GlobalYeast
Rangel, Franklin
GlobalYeast
Souza, Paula
GlobalYeast
Oki, Sergio
GlobalYeast
do Amaral, Marcelo
GlobalYeast

Bioethanol fermentation at industrial scale is typically carried out adhering to long-established standard operational practices that involve relatively little monitoring. Few properties of interest are routinely monitored if at all, providing a poor basis for informed decision making and real-time control strategies. Thus, there is an opportunity for development of on-line monitoring and control tools that can lead to better process insight and support informed decision-making. This work presents a model describing bioethanol fermentation by Saccharomyces cerevisiae and its application to monitor industrial fermentations. Our approach focuses on a first principles model with adaptive parameters that are estimated on-line with process data. The monitoring technique was implemented in an industrial bioethanol plant. Estimates from the model are presented and compared with offline analyses. Estimates from the model obtained on-line showed good agreement with off-line analyses.

16:00-17:00 WeBrAfCP.3
Towards a Model-Based Experimental Design of the Maturation Process of Biohybrid Heart Valves, pp. 121-128
Voß, Kirsten
RWTH Aachen University
Pyta, Lorenz
RWTH Aachen University
Gesenhues, Jonas
RWTH Aachen University
Mela, Petra
RWTH Aachen University
Schmitz-Rode, Thomas
RWTH Aachen University
Abel, Dirk
RWTH-Aachen University

Model-based experimental designs minimize the experimental effort while maximizing the amount of analyzable experimental data. In this paper, an initial mathematical model of the spatially distributed maturation process of tissue engineered heart valves is developed for a model-based experimental design. The model contains the state variables fibroblast amount, collagen concentration and elastin concentration. Based on the developed model, a variance-based sensitivity analysis using Sobol’s method is performed. The
results indicate that all model parameters influence the model solution, while the variance of the parameters related to fibroblast diffusion comprises an exceeding influence. Consequently, corresponding experiments should especially focus on those parameters.

16:00-17:00 WeBrACP.5

A Reduction Strategy to Simplify a Model of Sugar Metabolism for Application to a Large Panel of Genotypes, pp. 129-130

kanso, hussein INRA
Quilot-Turion, Bénédicte INRA
MEMAH, Mohamed-Mahmoud INRA
Bernard, Olivier INRA
Gouze, Jean-Luc INRA
Baldaazzi, Valentina INRA

Several studies have been conducted to understand the dynamic of primary metabolism in fruit by translating them into mathematics models. An ODE kinetic model of sugar metabolism has been developed by Desnoëe et al. (2018) to simulate the accumulation of different sugars during peach fruit development. Two major drawbacks of this model are (a) its number of parameters to calibrate and (b) its integration time that can be costly due to non-linearity and its time-dependent input functions. Together, these issues hamper the use of the model for a large panel of genotypes, for which few data are available. In this paper, we present a model reduction pipeline that combines different methods to overcome such two drawbacks. Thus, we combine multivariate sensitivity analysis, structural simplification and timescale-based approaches to simplify the number and the structure of ordinary differential equations of the model. The original and reduced models were compared for 10 genotypes. The reduced model not only reproduces the predictions of the original one but presents many advantages including numerical stability and shorter computational time allowing its calibration for 10 more genotypes.

16:00-17:00 WeBrACP.7

CISPER: Computational Identification of Switch Points (in a Metabolic Network) within an Environmental Range, pp. 133-134

Mairet, Francis Ifremer

A key challenge in systems biology is to identify, from the hundreds or thousands of molecules involved in a metabolic network, the key metabolites and the orientation of fluxes occurs. Here, we propose a method - called CISPER - to identify these switch points based on the analysis of a set of flux balance analysis (FBA) solutions. A metabolite is considered as a switch if the fluxes at this point are redirected in a different way when conditions change. After its presentation, the soundness of CISPER is shown with two case studies: - the central metabolism of the microalgae Tisochrysis lutea and the transition from aerobic to anaerobic conditions in the yeast Saccharomyces cerevisiae.

16:00-17:00 WeBrACP.8

SEML: A Simplified English Modeling Language for Constructing Biological Models in Julia, pp. 135-142

Varner, Jeff Cornell
Zhang, Zhiping Cornell University

Many markup languages can be used to encode biological networks, each with strengths and weaknesses. Model specifications written in these languages can then used, in conjunction with proprietary software packages e.g., MATLAB, or open community alternatives, to simulate the behavior of biological systems. In this study, we present the Simplified English Modeling Language (SEML) and associated compiler, as an alternative to existing approaches. SEML supports the specification of biological reaction systems in a simple natural language like syntax. Models encoded in SEML are transformed into executable code using a compiler written in the open-source Julia programming language. The compiler performs a sequence of operations, including tokenization, syntactic and semantic error checking, to convert SEML into an intermediate representation (IR). From the intermediate representation, the compiler then generates executable code in one of three programming languages: Julia, Python or MATLAB. Currently, SEML supports both kinetic and constraint-based model generation for signal transduction and metabolic modeling. In this study, we demonstrate SEML by modeling two proof-of-concept prototypical networks: a constraint-based model solved using flux balance analysis (FBA) and a kinetic model encoded as Ordinary Differential Equations (ODEs). SEML is a promising tool for encoding and sharing human-readable biological models, however it is still in its infancy. With further development, SEML has the potential to handle more unstructured natural language inputs, generate more complex models types and convert its natural language markup to currently used model interchange formats such systems biology markup language.
In this work we set the basis of a framework for automated design of gene regulatory networks in presence of intrinsic molecular noise. This framework combines a recently developed method for efficient simulation of stochastic gene regulatory networks with a global mixed integer nonlinear optimization algorithm. The capabilities of the proposed methodology are illustrated through the design of a synthetic gene switch in presence of molecular noise.

ThMo2T1.3

Global Stabilization of a Genetic Positive Feedback Loop Via the Design of a Synthetic Auto-Repression
Chambon, Lucie
Gouze, Jean-Luc
INRIA
INRIA

Gene positive feedback loops are essential for cell differentiation processes. They are accurately modeled with N-dimensional nonlinear monotone dynamical systems that display bi-stability: the two stable fixed points represent two distinct cell differentiated states, whereas the unstable fixed point is interpreted as a cell undifferentiated state. This paper shows that the synthetic design of a simple self-inhibition of one gene in the loop is able to globally stabilize the unstable fixed point of the network. This modification may lead to a promising cell dedifferentiation process during which cells regress from a specialized state to an earlier developmental state. Compared to a similar experiment designed for the Toggle Switch, this new synthetic circuit prevents the use of any input and measurement devices, reducing greatly the complexity of the biological set up. In order to take into account inherent biological uncertainties, the cell undifferentiated state is later considered as a region of the state space around the unstable fixed point and is shown to be globally attractive with the same simple synthetic modification of the loop. Some conditions are given such that all the possible fixed points of the circuit are confined in the undifferentiated region and the global results are proved with the theory of monotone dynamical systems.

ThMo2T1.4

Exploiting Ultrasensitivity for Biomolecular Implementation of a Control System without Error Detection
Montefusco, Francesco
BULAI, Iulia Martina
University of Padova
Department of Information Engineering, University of Padova, Italy

The application of engineering principles to understand and design biological systems is a powerful approach in systems and synthetic biology, respectively. In these fields, feedback control is widely used...
for achieving a better understanding of biological homeostasis. Recently, we have exploited this approach to investigate the role of ultrasensitivity, a common feature of biomolecular circuitry, for explaining the adaptive response dynamics observed in the yeast osmoregulatory response network. Here, we find that a generic control system working without error detection and implementing such ultrasensitive nonlinear dynamics allows achieving tunable adaptive responses: the system is able to track a reference signal that is not imposed externally, but it is determined by tunable threshold and slope characterizing the sigmoidal signal-response relationship of the controller. In particular, we show how the system exhibits adaptive dynamics by working around the point of high sensitivity of the sigmoidal response of the ultrasensitive controller. By performing a sensitivity analysis by changes of the nominal parameter values of the control system, we also show a good level of robust performance in terms of adaptation. Therefore, our analysis provides insights into how biology can measure a reference state and deviations from this (i.e. error) by exploiting the ultrasensitive response observed in many different biomolecular systems.

Reference Conditioning Anti-Windup for the Biomolecular Antithetic Controller, pp. 172-178

Nöbel Santos-Navarro, Fernando
Universitat Politècnica De Valencia, Spain
De Battista, Hernán
Universidad Nacional De La Plata - CONICET
Nuñez, Sebastián
Universidad Nacional De La Plata - CONICET
Picó, Jesús
Universitat Politècnica De Valencia, Spain

The design and implementation of biomolecular feedback control strategies embedded within large biomolecular synthetic systems is one of the key areas of Synthetic Biology. Many important challenges remain to be addressed. Among them, the lack of realizations of existing control algorithms through available biomolecular devices. Thus, proportional-integral controllers, one of the basic widely-used control strategies has been elusive for a long time. Recently, the antithetic sequestration-based motif has been shown to ensure robust perfect adaptation under mild assumptions and has been combined to implement proportional-integral feedback strategies. Yet, windup caused either by limitations in the process to be controlled or, most often, to restrictions in the actuator is a common problem of feedback control strategies with integral action. Saturation of signals is a limitation inherent to the biomolecular implementation of most circuits. Therefore, windup is a potential problem in biomolecular antithetic-based PI controllers. Reference conditioning, that is, dynamically providing a feasible set-point has been successfully used to tackle with the control of systems with control or state limitations. Here, we propose a reference conditioning scheme with application to the antithetic PI biomolecular controller. We show how the scheme is able to deal with windup due to large excursions in the desired set-point or limitations caused by an increased metabolic burden in the cell.

About Overyielding with Mixed Cultures in Batch Processes (I), pp. 179-184
Harmand, Jérôme
INRA
Rapaport, Alain
INRA
NIDELET, Thiibault
INRA

This paper investigates - via modeling - several possible explanations of overyielding observed in mixed cultures cultivated in batch reactors. It is rat shown that the classical model of competition of N species for a single resource cannot explain such overyielding. Then, three hypotheses are introduced and discussed at the light of numerical simulations.

FBA-Based Simulator of Saccharomyces Cerevisiae Fed-Batch Cultures Involving an Internal Unbalanced Metabolite, pp. 185-190
Plaza, José
Université Libre De Bruxelles.
Bogaerts, Philippe
Université Libre De Bruxelles

A dynamic macroscopic simulator based on Flux Balance Analysis (FBA) is proposed to predict the dynamics of biomass growth, substrate consumption (glucose and ammonium) and ethanol production in S. cerevisiae fed-batch cultures. It is based on a metabolic network containing the main metabolism of the yeast, an objective function aiming at maximizing the biomass growth, different inequalities corresponding to some biological assumptions such as glucose overflow metabolism and inequalities which link the fluxes to models of substrate uptake rates. Since it was not possible to accurately correlate the input fluxes with only the extracellular species concentration, a new variable is introduced in the uptake rate models using the information at intracellular level. We first determine the dynamics corresponding to the intracellular metabolite, namely alpha-ketoglutarate, and, in a second part, this new information is used for modelling the input flux rates. Secondly, all the information is integrated in a set of mass balances for building a simulator based only on the initial conditions of each species and the feeding rate. It is validated with direct and cross-validation. This model allows, on the one hand, reproducing the dynamics of extracellular species and, on the other hand, describing the accumulation of alpha-ketoglutarate.

Targeted Conversion of Protein and Glucose Waste Streams to Volatile Fatty Acids by Metabolic Models, pp. 191-196
Regueira, Alberte
Universidade De Santiago De Compostela
Bevilacqua, Riccardo
Universidade De Santiago De Compostela
Lema, Juan Manuel
Universidade De Santiago De Compostela
Carballa, Marta
Universidade De Santiago De Compostela
Mauricio-Iglesias, Miguel
Universidade De Santiago De Compostela

Mixed-culture fermentations are recognised as suitable processes to valorise organic wastes and convert them into added-value products. One of the main issues of these processes is that the stoichiometry of the fermentations is highly dependent on environmental conditions such as the pH or the concentrations of the different substrates. In this work we developed a mathematical model for the production of volatile fatty acids from wastes featuring high concentrations of carbohydrates and proteins. The model reproduces experimental results, predicting the tendencies of the product spectrum when varying pH values and at different proportions of carbohydrates and proteins in the feeding. This model can be the core of a tool for the computer-aided design of mixed-culture fermentations.

Model-Based Analysis and Optimisation of a Continuous Corynebacterium Glutamicum Bioprocess Utilizing Lignocellulosic Waste, pp. 197-202
Sinner, Peter
Vienna University of Technology
Kager, Julian
Vienna University of Technology
Daune, Sven
Vienna University of Technology
Herwig, Christoph
Vienna University of Technology

Lignocellulosic waste streams are an important sustainable alternative to conventional carbon sources for industrial
biotechnology. However, lacking quantitative knowledge on cultivation behavior hampers process design and optimization. Using an unstructured kinetic model describing the growth of wild-type *Corynebacterium glutamicum* on a lignocellulosic waste stream from pulping industry, we designed a continuous fermentation process with an optimized space time yield for biomass of 0.86 g L\(^{-1}\) h\(^{-1}\) and a residual concentration of metabolizable sugars in the effluent of less than 2 %. The model considers the growth on multiple interacting sugars and potentially inhibitory effects of lignocellulosic waste. After parameterization on historical data, the model was used to determine optimal setpoints of dilution rate and feed medium concentration. Sensitivity analysis of the model provided additional information on the importance of certain parameters during different process conditions and detected bottlenecks of strain physiology limiting the process design space. This model-based approach delivers valuable insights for process and strain engineering already at an early stage of bioprocess development.

12:06-12:30 ThMo2T2.5
**Modelling Bounded Random Fluctuations in Biological Systems: Application to the Chemostat Model with Two Species (1)**, pp. 203-208
Caraballo, Tomas  
Univ. of Seville  
López-de-la-Cruz, Javier  
Universidad De Sevilla  
Rapaport, Alain  
INRA

The chemostat model is used in many situations to represent biological systems in which micro-organisms grow on abiotic resources. Nevertheless, most of the times, the deterministic versions of this model are analyzed in spite of random fluctuations that frequently appear in real life ecosystems. We model and analyze random fluctuations on the input flow in the chemostat model, that are bounded inside a given interval that could be provided by practitioners. We use the Omstein-Uhlenbeck process which has already proved to be a suitable tool when modeling biological systems. In the present work, we consider the chemostat model with two competing species, for which the Competitive Exclusion Principle holds in absence of disturbances. We show that the kind of fluctuations on the input that we consider here allows the coexistence of species.

**ThAf1T1.1**
**Towards the Construction of GSMN-Based Community Model for an Oral Biofilm**, pp. 209-215
De Winter, Kjerstin  
KU Leuven  
Ghesquière, Justien  
KU Leuven  
Teughels, Wim  
KU Leuven  
Waldherr, Steffen  
KU Leuven  
Bernaerts, Kristel  
University of Leuven (KU Leuven)

Oral biofilms form on all hard and soft surfaces of the oral cavity. When the microbial balance in this biofilm is disturbed, pathogens can take the overhand, and this can lead to periodontitis (i.e. a chronic and inflammatory disease of the gum and tooth supporting tissues). In this work, a dual species community model containing one commensal bacterium and the most common periopathogen, is presented. The commensal bacterium is Streptococcus gordonii, the periopathogen is Porphyromonas gingivalis. Existing Genome-Scale Metabolic Models (GSMNs) are curated and transformed into planktonic Dynamic Flux Balance Analysis (dFBA) models in DFBAlab. In the planktonic model for *S. gordonii*, split ratio’s are used to ensure correct flux distributions between the glycolysis and the pentose phosphate pathway and around the pyruvate node. The split ratio’s are required to simulate the suboptimal growth behaviour of this bacterium. Simulation results for the planktonic *S. gordonii* model are compared to experiments for pure cultures. The planktonic *P. gingivalis* model gives feasible results for biomass growth and nutrient uptake. Finally, both planktonic models are transformed into a biofilm model in DFBAlab by introduction of nutrient gradients over the depth of the biofilm. This first oral biofilm model predicted the partitioning of both bacteria in the biofilm, similar to what has been described in literature.

14:24-14:48 ThAf1T1.2
**Characterizing and Ranking Computed Metabolic Engineering Strategies**, pp. 216-216
Schneider, Philipp  
Max Planck Institute for Dynamics of Complex Technical Systems  
Klamt, Steffen  
Max Planck Institute for Dynamics of Complex Technical Systems

The computation of metabolic intervention strategies from a mathematical model, is a key component of an integrated metabolic engineering approach. A broad range of methods has been developed for this task, including bilevel optimization routines and the framework of Minimal Cut Sets (MCSs). Some of them may return a large pool of possible intervention strategies from which the most suitable strategy must be selected. Here we present 10 criteria to characterize and rank a given pool of intervention strategies computed for growth-coupled product synthesis [1]. Some criteria are straightforward, for example, the number of interventions, the maximal growth rate and the guaranteed minimum product yield. Less intuitive are methods to assess the robustness of intervention strategies, e.g. with respect to loss of coupling or the undesired accumulation of metabolites. We also rank intervention strategies higher if they allow for higher thermodynamic driving forces or rely on flux re-routing in the central metabolism. Furthermore, strategies that have a significant overlap with alternative solutions are favored as they provide flexibility in implementation. We finally introduce the notion of equivalence classes for grouping intervention strategies with identical solution spaces. We demonstrate applicability of our approach by assessing minimal cut sets computed in a genome-scale model of *E.coli* for the growth-coupled synthesis of l-methionine and of the heterologous product 1,4-butanediol. Finally we give an outlook on a new and comprehensive computational strain design method, based on the concept of minimal cut sets. The presented method allows the definition of multiple desired and undesired features and opens the door to finding intervention strategies that are not only knock-out based, but also make use of insertions and auxiliary substrates.


14:48-15:12 ThAf1T1.3
**Towards Metabolic Optimization of CHO Cells: In Silico Improvement of Culture Medium**, pp. 217-218
Hamdi, Anis  
University of Minho  
Santos, Sophia  
Centre of Biological Engineering  
Rocha, Isabel  
University of Minho

The emergence of "omics" tools and bioinformatics potentiated the development of new strategies to optimize several expression platforms, in particular mammalian cell lines, being CHO cells one of the most commonly used cell line for the production of recombinant proteins. Foremost, computational modelling combined with CHO cell omics data can help optimizing growth parameters, as well as improving the final product yield. In this context, CHO genome scale metabolic model (GSSM) was used in order to study the metabolic behavior of the cells in response to variations in environmental constraints, such as amino acids levels, targeting the development of a novel chemically defined culture medium formulation for CHO cells. To study this influence, GSSM combined with an in-house developed algorithm was employed to determine the minimal medium formulation to sustain growth for non-recombinant as well as for recombinant CHO cells lines. Optflux tool was used to predict metabolic behavior of the cells in response to the environmental constraints tested. Based on in silico predictions, growth yield value was improved 2.8 times and 1.8 times, respectively, for non-recombinant and recombinant CHO cells lines comparing to previously reported data. Furthermore, toxic by-products such as ammonium were decreased to their lowest levels. In silico-based approaches for medium optimization are powerful tools for predicting the metabolic interconnexion in the cell
and for selecting potential experimental conditions for further validation in bioreactor systems.

15:12-15:36    ThAf1T1.4
Metabolic Flux Inference with Thermodynamic Constraints and 13C-MFA, pp. 219-220

Salida, Joana University of Groningen
Muntoni, Anna Paola Laboratoire De Physique Théorique, Ecole Normale Supérieure, Par
De Martino, Daniele Institute Jozef Stefan
Hubmann, Georg Laboratory of Molecular Cell Biology, Department of Biology, Ins
Bastian, Niebel Cyoss GmbH
Braunstein, Alfredo Politecnico Di Torino
Miliais Argeitis, Andreas University of Groningen
Heinemann, Matthias University of Groningen

Metabolism quantification is essential for applied and fundamental metabolic research. Metabolic fluxes cannot be experimentally measured, thus need to be inferred from experimental data by mathematical models. Currently the most used approach is 13C-metabolic-flux-analysis (13C-MFA). However, it has limitations on the size of the solvable networks and heuristic assumptions on reaction direction and reversibility. To overcome this, we present a new multi-step flux inference method based on thermodynamic constraints and 13C-MFA. First, a thermodynamic and stoichiometric metabolic model (TSM) is fitted to extracellular fluxes and metabolite concentrations data to estimate a thermodynamically consistent set of standard Gibbs energies. Bounds for fluxes (v), Gibbs energies (ΔG) and concentrations (c) are estimated by variability analysis. As the space of v, ΔG and c defined by the bounds and TSM constraints is non-convex, we developed a new sampling approach to sample this space. The space is divided in two convex spaces: one using the mass balance constraint with fluxes as variables (A); another using thermodynamic constraints with c and ΔG as variables (B). Conditional on each flux point v in A, a subset of points in B (B_v) is determined. In this way, A is uniformly sampled under the condition of non-empty B_v. A and B are sampled with a Hit-and-Run Markov Chain Monte Carlo algorithm. Finally, each v is scored with the residual of the fitting of a stoichiometric model with 13C-labelling data, using 13CFLUX2. The flux space is reduced by selecting the samples with best score. We applied the method to a 258 reactions' network of budding yeast. The thermodynamic constraints reduced the flux ranges by 57% more than a stoichiometric model and there was a 45% increase in determined reactions' directions. The 13C-data can fit a flux space volume decrease of 17%. Moreover, we identified a number of reactions in the network as unidirectional. Overall, we present a pipeline that combines the power of thermodynamic constraint-based models with 13C-data. This can narrow the flux space for realistic scale metabolic network without assumptions on reaction directions and reversibility.

15:36-16:00    ThAf1T1.5
Predicting Dynamic Metabolic Flux Distributions in Wine Fermentation, pp. 221-222

Henriques, David IIM-CSIC
Minebois, Romain IATA-CSIC
Pérez-Torrado, Roberto IATA-CSIC
Querol, Amparo IATA-CSIC
Balsa-Canto, Eva CSIC

Dynamic flux balance analysis (DFBA) is one of the most widely used approaches towards the design of bioprocesses. DFBA combines genome-scale metabolic network analysis with the dynamic model of the extracellular environment. The model can be solved using an optimisation procedure which assumes a cellular objective: typically the growth rate maximisation. In this work, we considered an iterative identification procedure which combines global optimisers with FBA under a variable step size integrator and a bootstrap based approach to predict the dynamics of cellular fluxes in fermentation processes. In particular, we considered wine fermentations led by Saccharomyces cerevisiae and Saccharomyces uvarum strains at sub-optimal temperatures with a focus on the quantitative prediction of the aroma profile. The iterative procedure led us to conclude that growth maximisation is not the single cellular objective throughout the fermentation. Indeed, protein turnover and the dynamics of biomass play a critical role to predict the dynamics of the synthesis of aromas. These results open new venues to decipher the metabolism of bacteria and yeast in food fermentation processes.

14:00-14:24    ThAf1T2
Modelling of Complex Biological Systems II (Regular Session)

Chair: di Bernardo, Diego
Co-Chair: Waldherr, Steffen
ThAf1T2.1
Dirac Mixture Distributions for the Approximation of Mixed Effects Models, pp. 223-229

Wang, Dantong Helmholt Zentrum, München
Stapor, Paul Helmholt Zentrum München
Hasenauer, Jan University of Bonn

Mixed effect modeling is widely used to study cell-to-cell and patient-to-patient variability. The population statistics of mixed effect models is usually approximated using Dirac mixtures. Our results indicate that for given number of points, the method combined with the Cramér-von Mises distance method allows a flexible number of points and a more accurate approximation for non-linear problems.

14:24-14:48    ThAf1T2.2
Individual-Based Modeling Explains Effects of TRAIL Treatment in Cancer Cells, pp. 230-235

Imig, Dirke University of Stuttgart
Pollak, Nadine Institute for Systems Theory and Automatic Control, University O
Weiß, Felix Institute for Systems Theory and Automatic Control
Morrison, Markus Institute of Cell Biology and Immunology, University of Stuttgart
Aligower, Frank University of Stuttgart

The endogenous ligand TRAIL induces cell death and constitutes a promising molecule for cancer therapies. However, reasons for TRAIL-insensitivity of various tumor-based cancer cell lines remain unclear. In this paper, we introduce a complex individual-based model that captures the major effects of TRAIL in a heterogeneous cancer cell population. First, we adapted an existing TRAIL-signaling model to recent insights. The improved model was integrated into an established population framework. Next, we included a cell cycle-dependent upregulation of anti-apoptotic signaling proteins, such as Bcl-2. Afterwards, specific model parameters were adapted to fit physiological cell counts and death timing during TRAIL stimulation. With help of the adapted population model, we observed a phenotypical cell cycle dependence of death kinetics. Cells died on average slightly faster and more efficiently when treated in the first half of the cell cycle. Lastly, we focused on changes in protein distributions during a TRAIL treatment. We predicted the anti-apoptotic protein XIAP and the pro-apoptotic protein Bid to undergo the highest changes on average. Surviving cells exhibited decreased amounts of XIAP whereas synthesis rates of XIAP increased. Initial flow cytometry experiments confirmed the predicted drop of XIAP qualitatively. After TRAIL wash out, XIAP amounts recovered fast, indicating a correct prediction of high synthesis rates. Overall, the developed model represents a versatile tool for gaining holistic insights into TRAIL-based cancer treatments.
The transcription factor EB (TFEB) is a key component of the transcriptional regulation of lysosomal biogenesis and autophagy in response to starvation. Autophagy is a self-degradative process activated by cells to survive during nutrient deficiency. In normal conditions, TFEB is sequestered in the cytoplasm through phosphorylation. Following starvation, TFEB is dephosphorylated and translocates into the nucleus binding DNA and promoting the activation of its target genes. Here, we developed a quantitative dynamical model of TFEB regulation to elucidate the biological mechanisms driving its regulation. A two-compartment model (nucleus and cytoplasm) was developed where two different species (de/phosphorylated TFEB) for each compartment are considered. Both de/phosphorylation and transport are modeled as first order kinetics whereas the input (the lack of nutrients) acts by changing the de/phosphorylation rates. Model parameters were identified by fitting experimental data including time-series single cells data acquired via a microfluidics-based platform. The model was able to correctly predict experimental data and was used to hypothesize the existence of a negative feedback loop driving TFEB regulation mediated by autophagy.

15:12-15:36  ThA1T.4
Population Balance Modeling of Activated Sludge Microcolony Growth and Breakage, pp. 242-243
Totos, Niccolo  KU Leuven
Christiaens, an-sofe  KU Leuven
Smets, Ise  KU Leuven, Department of Chemical Engineering, CREAeS
Waldherr, Steffen  KU Leuven

Population balance equations (PBeS) is a mathematical framework suited to represent heterogeneous particulate systems. An example of such systems are microcolonies of activated sludge bacteria, particles whose size distribution takes a central role in waste water treatment. In this work we present an application of PBeS where the growth and the breakage of microcolonies are influenced by intracellular events as well as processes happening at the level of the whole reactor. Moreover, we show that this framework allows us to represent the heterogeneous metabolic modes of growth present in the population.

15:36-16:00  ThA1T.5
Simple Nonlinear Models for Glucose-Insulin Dynamics: Application to Intraperitoneal Insulin Infusion, pp. 244-249
Lopez-Zazueta, Claudia  NTNU
Stavdahl, Øyvind  Norwegian University of Science and Technology (NTNU)
Fougner, Anders Lyngvi  Norwegian University of Science and Technology

The design of a model-based control method for an Artificial Pancreas requires a relatively simple and identifiable mathematical model to control glucose levels through hormone delivery. In this work we introduce new, simple nonlinear models to simulate data from experiments where insulin boluses are administrated in the peritoneal cavity. The models account for the delay between insulin administration and its nonlinear transport to other compartments. They were calibrated using experimental data from pigs. The results show that the suggested models are able to describe the data well, with average BIC value of 145. Moreover, the new models were compared with a common linear model which was not able to describe the data well, with BIC value of 920. They were also compared with a common nonlinear model which failed to represent insulin increases in the data and had BIC value of 637. Finally, profile likelihoods were applied for assessing the identifiability of one of the new models.
relationships between model parameters, without explicitly modeling context. To characterise relationships between model parameters, we compute the geometry of the feasible parameter spaces, using set-membership estimation. These parameter spaces are more compatible with a bottom-up approach to constructing biocircuits, as they offer more of the design space and allow the greater freedom in selection of circuit components. They are also richer in information about relationships between parameters than their scalar counterparts, as they enclose all feasible combinations of scalar parameters.

The analysis of the relationships is split into two types, intra-context and inter-context. By intra-context we mean analysis of the relationships between model parameters that are optimised for the same context. By inter-context we mean a comparative analysis of the relationships between model parameters that are optimised for different contexts. We hypothesise that such analyses may be used to account for context during the biocircuit design stage.

16:00-17:00 ThBraICP.4

The Development of a Fed-Batch Corynebacterium Glutamicum Fermentation Model (I), pp. 260-266

Lira Parada, Pedro Antonio, Pettersen, Even, Pérez-García, Fernando, Bar, Nadav S.

Norwegian University of Science and Technology NTNU, Univesity of Newcastle

Fed-batch bioreactors are multiple input, multiple output non-linear systems with a central role in the production of antimicrobials, fine-chemicals and desirable products of pharmaceutical industry, and as such industrial microbial bio-catalytic processes require understanding of the microorganism, the bioreactor, and the set of differential equations that allow the description of the fermentation system. In the present study, we show our preliminary modelling results of growth of Corynebacterium glutamicum wild type strain ATCC13032 in a single sugar system. The differential equations consider an unstructured model of C. glutamicum to describe the liquid and gas phase, and the results suggest that is possible to model the titers in the liquid and concentrations in the gas phase for the simple sugar system. We anticipate that these results are the basis for further C. glutamicum fed-batch reactor modelling with other carbon sources, complex mixtures of them, implementation of novel control and optimization structures, and the development of state estimators from in-situ measurements.

16:00-17:00 ThBraICP.5

A Rule-Based Approach for Model Testing and Refinement (I), pp. 267-268

Schade, Sophia, Muradyan, Artur, Kessler, Thomas, Lange, Bodo, Wierling, Christoph


Mechanistic models of cellular signaling pathways are constructed based on functional knowledge of regulatory molecular mechanisms derived from scientific publications and publicly available data resources. The development of accurate computational models based on this accumulating knowledge base requires evaluation of the model’s topological and functional structure, as well as qualitative determination of whether it reflects biological expectations. Here, we present an in silico approach for testing the structural integrity of these computational models. Using the Hedgehog signaling pathway as an example, we simulate a range of different perturbation scenarios and quantitatively compare the predicted effect with biological expectations. First, we specify model-inherent driver and regulatory components as well as related downstream readouts. Based on these specifications a panel of virtual experiments is defined using specific rules (e.g. perturbing individual positive or negative regulators). Next, we simulate these experiments for the given model using a Monte Carlo approach (Wierling et al., Mutat Res. 2012, 746(2):163-70). Finally, the simulation results are visualized and analyzed in order to compare and validate the qualitative predictions with published observations and experimental datasets. Any inconsistencies between predictions and experimental results help to identify model limitations, which can be subsequently addressed via iterative rounds of model refinement and validation. The approach presented here provides a practical and efficient method for improving model integrity on both the structural and functional levels and can be employed at any stage of model extension and troubleshooting.

16:00-17:00 ThBraICP.6

Simulation of Intracellular Calcium Release in Heart Cells, pp. 269-274

Vysma, Morris, Welsh, James, Laver, Derek

University of Newcastle

Cyclic calcium release and uptake in heart cells has an important role in heart rhythm and contraction, and it is known that the malfregulation of calcium release is a predictor for cardiac arrhythmia. A model of this calcium release process was proposed, which consists of a large number of discrete calcium release sites, each involving stiff, stochastic, and non-linear systems. In this paper we have developed a simulation of this calcium release model, which is parallel across the problem. The simulation is developed in a CUDA framework to be solved using GPUs. Computational efficiency is enhanced by using a DIIRK solver and taking advantage of the sparsity of the Jacobian. The output is shown to display behaviour similar to empirical observations, in particular displaying behaviour known as calcium waves.

16:00-17:00 ThBraICP.7

Reconstruction and Analysis of Genomic-Scale Metabolic Models of Industrial Escherichia Coli Strains, pp. 275-276

Alvarez Villanueva, Patricia, Corbin, Paola, Ruiz, Mario, Peretó, Juli

I2SysBio University of Valencia-CIC, I2SysBio University of Valencia-CIC, I2SysBio University of Valencia-CIC

Genome-scale models (GEM) of microbial metabolism may be key assets for the biotechnology industry due to their ability to predict and describe microbial phenotypic characteristics. Here we present a diversity of strategies, including Possibilistic Flux Analysis, for validation of the constraint-based metabolic models of nine industrially relevant Escherichia coli strains. Furthermore, a model of a different E. coli strain with probiotic capabilities has been established and validated. These models and strategies will be of great value for identifying products of biotechnological interest.

16:00-17:00 ThBraICP.8

A Low Cost, Open Source Turbidostat Design for In-Vivo Control Experiments in Synthetic Biology, pp. 277-281

Guarino, Agostino, Shannon, Barbara Mary, Marucci, Lucia, Grierson, Claire, Savery, Nigel

 Universita’ Degli Studi Di Napoli “Federico II”, University of Bristol, University of Bristol, University of Bristol

Continuous culture platforms are required to characterise the dynamics of new engineered systems in synthetic biology. In this paper, we review existing turbidostat platforms before describing the design and implementation of our new flexible and low-cost turbidostat for in-vivo control experiments. We provide preliminary experimental results on controlling the optical density of a bacterial culture. We also discuss the potential extensions to our design for the development of in-vivo multicellular control experiments.

16:00-17:00 ThBraICP.9

Model Mismatch in Multi-Objectiveoptimisation and Trade-Off Ordering Preservation, pp. 282-287

Reynoso-Meza, Gilberto

Pontificia Universidade Católica
Multi-objective optimisation is a valuable tool for tuning dynamical systems when simultaneous optimisation performance objectives are in conflict. When the goal is tuning the parameters of a synthetic biology device, mismatch between the model implemented in silico—a more or less coarse simplification of the real system—and the actual in vivo implementation might lead to a disagreement between the in silico and in vivo design objectives for a given solution from the Pareto front. Here, we propose an iterative closed-loop multi-objective optimisation approach where the new information provided by the difference between the in silico Pareto front and its in vivo implementation is used to improve the parametric model. This aims to minimise the discrepancies between in silico and in vivo performance objectives while preserving the trade-off order among solutions. As a proof-of-concept we consider the problem of tuning a synthetic gene circuit used as a feedforward-feedback controller for the expression of a protein of interest. We use an extended parametric model of the gene synthetic circuit to represent the in vivo set up and a simplified one for the in silico one.

A System Biology Approach Revealed the Nature and the Cause of the Different Metabolic Features of Weak and Strong Antibiotic Producers of the Streptomyces Genus, pp. 288-288

Introduction: Streptomycetes are efficient producers of chemically diverse bio-active molecules useful to human health including life-saving antibiotics. The biosynthesis of these so called “secondary metabolites” usually occurs in the period of slow or no growth. It is thought to be triggered by nutritional limitations, especially in phosphate, that are correlating with energy shortage. Despite numerous important scientific contributions over the past 40 years, a systemic understanding of the regulation of the biosynthesis and of the function of these bio-active metabolites for the producing bacteria remain incomplete. Methods: The model strains, Streptomyces lividans and Streptomyces coelicolor, are extensively studied in the field to address these questions. These closely related species possess identical biosynthetic pathways directing the synthesis of three well characterized secondary metabolites (CDA, RED and ACT) but only S. coelicolor expresses them at a high level. A comparative analysis of the proteomes of these strains, grown on phosphate limited R2YE medium, with glucose as main carbon source, was carried out in order to establish the specific metabolic features linked to weak and strong antibiotic production. Results: This study revealed the nature and cause of the distinct metabolic features underpinning the different “biosynthetic abilities” of these strains. It also indicated that the produced antibiotics play a role in the regulation of the energetic metabolism of the producing bacteria in conditions where phosphate is scarce. Conclusions: A better understanding of the regulation of antibiotic biosynthesis and of the role of the antibiotics in the physiology of their producers is important to conceive clever strategies to access the great metabolic diversity encoded in the numerous silent biosynthetic pathways present in the Streptomyces genomes. Indeed, the discovery of novel antibiotics has now become an urgent need to combat the spreading of pathogenic bacteria resistant to most antibiotics in current use.
We studied rhythmic systems, it is more confident even if the network model to formulate guidelines for efficient resource management. Quantity and systems perturbations are addressed, thereby forming a novel, multifactorial evaluation framework in order to highlight recent and successful network inference strategies under a heterogeneous experimental framework. This paper assesses the performance of recent and successful network inference algorithms due to time series data. However, the applicability and contrast for the non-rhythmic systems, increasing the number of perturbation experiments yielded better results than increasing the sampling frequency. We expect that future benchmark and algorithm design will integrate such multifactorial considerations to promote their widespread and conscientious usage.

Accurate model calibration is essential for model-based design of synthetic gene regulatory networks. Optimal experimental design (OED) techniques can be used to efficiently decrease parameter uncertainty. However, many biological networks of interest exhibit multimodal response functions due to multistability. These models are incompatible with traditional OED approaches that have been developed for models with mono-modal error distributions. In this work we propose an OED approach for a gene expression model that exhibits bistability via a saddle-node bifurcation with respect to an experimental input. We demonstrate construction of an approximate likelihood and derive the corresponding Fisher information matrix to cross-validate the switching probabilities between the stable equilibria. We then use this Fisher information matrix to work in this area, we do not rely on fitting a full model to promote their widespread and conscientious usage.

In the past years, many computational methods have been developed to infer the structure of gene regulatory networks from time series data. However, the applicability and accuracy of such algorithms remain unclear due to experimental heterogeneity. This paper assesses the performance of recent and successful network inference strategies under a novel, multifactorial evaluation framework. In order to highlight pragmatic tradeoffs in experimental design, the effects of data quantity and systems perturbations are addressed, thereby formulating guidelines for efficient resource management.

Realistic data were generated from six widely used benchmark models of rhythmic and non-rhythmic gene regulatory systems with random perturbations mimicking the effect of gene knock-out or chemical treatments. Then, time series data of increasing lengths were provided to five state-of-the-art network inference algorithms representing distinctive mathematical paradigms. The performances of such network reconstruction methodologies are uncovered under various experimental conditions. We report that the algorithms do not benefit equally from data increments. Furthermore, at least for the studied rhythmic system, it is more profitable for network inference strategies to be run on long time series rather than short time series with multiple perturbations. By contrast, for the non-rhythmic systems, increasing the number of perturbation experiments yielded better results than increasing the sampling frequency. We expect that future benchmark and algorithm design would integrate such multifactorial considerations to promote their widespread and conscientious usage.

Technical Program for Friday October 18, 2019

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<td>Auditorio Cubo Azul (Blue Cube’s Auditorium)</td>
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<td>Network Inference and Modelling</td>
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<td>Keynote 4. Small Multicellular Cohorts Are Engineered to Function As a Distributed Detector of Rare Multivariate Events. Daniel Georgiev, Founder and CEO, XENO Cell Innovations S.r.o</td>
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A Multifactorial Evaluation Framework for Gene Regulatory Network Reconstruction, pp. 296-302

Mombaerts, Laurent
Université Du Luxembourg
Aalto, Atte Erkko Juhani
University of Luxembourg
Markdahl, Johan
Royal Institute of Technology
Goncalves, Jorge M.
University of Luxembourg

In the past years, many computational methods have been developed to infer the structure of gene regulatory networks from time series data. However, the applicability and accuracy of such algorithms remain unclear due to experimental heterogeneity. This paper assesses the performance of recent and successful network inference strategies. Table 1 presents algorithms that are two distinctive mathematical paradigms. The performances of such network reconstruction methodologies are uncovered under various experimental conditions. We report that the algorithms do not benefit equally from data increments. Furthermore, at least for the studied rhythmic systems, it is more profitable for network inference strategies to be run on long time series rather than short time series with multiple perturbations. By contrast, for the non-rhythmic systems, increasing the number of perturbation experiments yielded better results than increasing the sampling frequency. We expect that future benchmark and algorithm design would integrate such multifactorial considerations to promote their widespread and conscientious usage.

DISCOPOLIS : An Algorithm for Uniform Sampling of Metabolic Flux Distributions Via Iterative Sequences of Linear Programs, pp. 305-310

Bogaerts, Philippe
Université Libre De Bruxelles
Rooman, Marianne
Université Libre De Bruxelles

In the past years, many computational methods have been developed to infer the structure of gene regulatory networks from time series data. However, the applicability and accuracy of such algorithms remain unclear due to experimental heterogeneity. This paper assesses the performance of recent and successful network inference strategies under a novel, multifactorial evaluation framework in order to highlight pragmatic tradeoffs in experimental design. The effects of data quantity and systems perturbations are addressed, thereby formulating guidelines for efficient resource management.
measurements. After reduction of the flux space based on the available equality constraints, the admissible reduced fluxes belong to a convex polytope defined by the intersection of half-planes representing the inequality constraints (e.g., upper and lower bounds of the fluxes). Random uniform sampling of this polytope allows building marginal distributions for each flux and computing the mean solution representative of the mean metabolism exhibited by the studied organism. This contribution proposes a new algorithm based on Discrete Sampling of Convex Polytopes via Linear program Iterative Sequences (DISCOPOLIS), in which the linear programs are iteratively used to constrain the solutions inside the polytope, taking into account all the previously estimated fluxes. The solutions are weighted to ensure sampling uniformity.

FrMo2T2 Salón de Actos Cubo Rojo (Red Cube's Events Room)
Control and Optimisation of Microalgae (Invited Session)
Chair: Bar, Nadav S. Norwegian Univ of Science and Technology
Co-Chair: Vande Wouwer, Alain
Organizer: Bernard, Olivier INRIA
Organizer: Bar, Nadav S. Norwegian Univ of Science and Technology
10:15-10:39 FrMo2T2.1 A Physiologically Structured Equation to Consider Quota Heterogeneity in the Droop Model (I), pp. 311-316
Mairet, Francis Ifremer
Baron, Régis IFREMER
The Droop model allows to represent microalgae growth limited by a nutrient, using a cell quota (also referred to as variable-yield) approach. Single-cell measurements have revealed quota heterogeneity in phytoplankton collected from field studies. Such heterogeneity can be due, among other factors, to spatial structure (e.g., in biogeochemical cycles in the ocean, or for photobioreactors connected in series). Nonetheless, quota heterogeneity is generally omitted in modelling studies, using an average quota approach, or included in size-structured or individual-based models. Here, we propose a distributed Droop equation to tackle this problem, considering subpopulation growth -in line with Droop macroscopic view- rather than cell division dynamics. We provide analytical solutions for two case studies. First, we consider a constant substrate level can be directly controlled. An optimal control model is derived from the classical Droop model, assuming the substrate level can be directly controlled. An optimal control problem (OCP) is formulated, with the objective of finding the substrate concentration which would maximize the fraction of the variable cell quota approach, and photoacclimation models, we build a mathematical model for describing microalgae growth under limitation by these resources. The model is calibrated with a data set from the literature. Then, by numerical simulations, we find that under constant operation of the culture and constant environmental conditions (illumination, temperature, pH, etc.), solutions of the model approach towards either a positive or an extinction steady state. Based on the positive steady state, and in the context of wastewater treatment, we evaluate the capacity of microalgae to remove contaminants. We showed that the impact of the depth, of the incident light intensity, and the dilution rate (or hydraulic retention time) have a crucial role on the optimization of the nutrient removal efficiency.

11:03-11:27 FrMo2T2.3 Quantifying the Potential of Microalgae to Remove Nutrients from Wastewater (I), pp. 323-328
Martinez, Carlos INRIA Sophia-Antipolis
Mairet, Francis Ifremer
Plaza, Luis Universidad Técnica Federico Santa María
Sciandra, Antoine LOV
Bernard, Olivier INRIA
The main resources limiting microalgae growth are typically phosphorus, nitrogen, and light. Based on the theory of the light limited chemostat, the variable cell quota approach, and photoacclimation models, we build a mathematical model for describing microalgae growth under limitation by these resources. The model is calibrated with a data set from the literature. Then, by numerical simulations, we find that under constant operation of the culture and constant environmental conditions (illumination, temperature, pH, etc.), solutions of the model approach towards either a positive or an extinction steady state. Based on the positive steady state, and in the context of wastewater treatment, we evaluate the capacity of microalgae to remove contaminants. We showed that the impact of the depth, of the incident light intensity, and the dilution rate (or hydraulic retention time) have a crucial role on the optimization of the nutrient removal efficiency.

11:27-11:51 FrMo2T2.4 Optimization of Microalgae Selection: Highlighting Turnpike Features (I), pp. 329-333
Djema, Walid INRIA
Bernard, Olivier INRIA
Giraldi, Laetitia Université Cote d'Azur, LJAD, INRIA Sophia-Antipolis
We consider a simplified dynamical system to represent the competition between two species of microalgae in a chemostat. The model is derived from the classical Droop model, assuming the substrate level can be directly controlled. An optimal control problem (OCP) is formulated, with the objective of finding the substrate concentration which would maximize the fraction of the species of interest over a fixed finite time-window. We characterize the substrate-based control strategy that steers the model trajectories and achieves species separation. Our objective is to highlight through a numerical optimal-synthesis - based on direct optimal control tools - the existence of a turnpike feature that appears in the optimal control law as well as in the optimal model trajectories and their co-states.

10:39-11:03 FrMo2T2.2 Extremum-Seeking for Micro-Algae Biomass Productivity Maximization: An Experimental Validation (I), pp. 317-322
Feudjo Letchindjo, Christian University of Mons
Gabin
Dewasme, Laurent Université De Mons
Vande Wouwer, Alain Université De Mons
This paper presents experimental results of a lab-scale implementation of an extremum seeking control strategy for maximizing the biomass productivity of cultures of the micro-algae <i>Dunaliella tertiolecta</i> in a flat-panel photobioreactor operated in continuous mode. The real-time optimization is based on a recursive least squares adaptation where the input (Dilution rate)/output (Biomass concentration) relation is approximated by a linear Hammerstein regression from which a productivity gradient estimate can be inferred. Lab-scale instrumentation and operating conditions are described and the results of two experiments are presented. They demonstrate the fast convergence of the extremum seeking scheme and practical considerations related to stability are discussed.
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<td>ThBrAfCP.2, ThBrAfCP.3, ThBrAfCP.8, ThBrAfCP.9, ThMo2T1.1, ThMo2T1.2, ThMo2T1.5, WeAf1T1.1, WeAf1T1.2, WeAf1T1.4, WeAf1T1.5, WeBrAfCP.9, WeMo2T1.1, WeMo2T1.2, WeMo2T1.3, WeMo2T1.4, WeMo2T1.5</td>
</tr>
<tr>
<td>S</td>
<td>Systems biology for (red, green, blue and white) biotechnology</td>
<td>ThAf1T1.5, ThAf1T2.4, ThBrAfCP.4, ThBrAfCP.7, ThBrAfCP.10, ThMo2T2.3, ThMo2T2.4, WeBrAfCP.5, WeBrAfCP.7</td>
</tr>
<tr>
<td>S</td>
<td>Systems medicine</td>
<td>ThAf1T1.3, ThAf1T2.5, WeAf1T2.5</td>
</tr>
</tbody>
</table>
Maps

Universitat Politècnica de València (UPV)
CPI Building (8B), Hall Cubo Azul (Blue Cube’s Hall)
Camino de Vera (Avinguda dels Tarongers), s/n
46022 València
SPAIN
(Entrance from street Fausto Elio)

UPV campus is located some 4 Km northeast of València old town.

UPV campus. CPI building 8B marked with an arrow. Nearest bus and Tram stops are shown.
CPI building 8B. Blue Cube (Cubo azul).

CPI is a singular and nice building, but it's not easy to get your bearings. The best way for arriving to the conference desk is to take one of the 2 panoramic lifts to the 3rd floor (they are located inside the CPI, at level 0). Then turn to the right, walking on an external wooden ground, until you arrive to the blue cube (Cubo Azul).

You will have indicators around the building for your orientation.