IFAC FOSBE 2019
INTERNATIONAL FEDERATION OF AUTOMATIC CONTROL
València, 15 - 18 October

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

Workshop 1	Workshop 2	Workshop 3
15:00-18:30 TuAf1T1 Room Aprende Workshop 1: Analyzing and Redesigning Metabolic Networks with CellNetAnalyzer	15:00-18:30 TuAf1T2 Room Debate Workshop 2: Multi-Omics Data and Multiscale Modelling in Winemaking	15:00-18:30 TuAf1T3 Room Descubre Workshop 3: Standarization for Synthetic Biology
18:30-20:00 TuAf2Wc, Hall Cubo Azul (Blue Cube's Hall), Welcome Reception		

Wednesday October 16, 2019

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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 València, 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 València. 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 València'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 València, 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 València.

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

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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Mustafa Khammash	CH	Giulia Giordano	NL
Chuanhou Gao	CN	Nadav Bar	NO
Steffen Klamt	DE	Eugenio Ferreira	PT
Olaf Worlkenhauer	DE	Filippo Menolascina	UK
Jan Hasenauer	DE	Diego Oyarzún	UK
Nicole Radde	DE	Guy-Bart Stan	UK
Nikolaus Sonnenschein	DE	Angel Goñi	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
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Olivier Bernard	FR	Hana El-Samad	US
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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 preceeded 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.

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

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 thoughout 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:

Type	Presentation time	Discussion time
Plenary	50 minutes	6 minutes
Keynote	40 minutes	5 minutes
Regular	20 minutes	4 minutes

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

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 Thiele
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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18:30-20:00 TuAf2Wc, Hall Cubo Azul (Blue Cube's Hall) **Welcome Reception**		

Program and Abstracts Wednesday October 16

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09:00-10:00 WeMo1P Auditorio Cubo Azul (Blue Cube's Auditorium) 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	
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17:00-17:45 WeAf2P Auditorio Cubo Azul (Blue Cube's Auditorium) Keynote 1. Modelling for Systems Medicine. Neda Bagheri, McCormick School of Eng. & Applied Science, Northwestern University	

Technical Program for Wednesday October 16, 2019

WeMo2T1 Auditorio Cubo Azul (Blue Cube's Auditorium)

Computational Design of Biomolecular Circuits (Invited Session)

Chair: Oyarzún, Diego A.	University of Edinburgh
Co-Chair: Otero-Muras, Irene	IIM-CSIC
Organizer: Oyarzún, Diego A.	University of Edinburgh
Organizer: Otero-Muras, Irene	IIM-CSIC

10:30-10:54 WeMo2T1.1

Biomolecular Signal Tracker with Fast Time Response (I), pp. 1-6

De Battista, Hernán	Universidad Nacional De La Plata - CONICET
Picó, Jesús	Universitat Politecnica De Valencia
Pico-Marco, Enric	Technical University of Valencia
Vignoni, Alejandro	Universitat Politècnica De Valencia

Signal tracking and the related signal derivative estimation are key pieces in feedback control engineered systems. In this work we present a synthetic biomolecular circuit that performs signal tracking with high precision under mild conditions on its parameters. The circuit contains two antithetic motifs in feedback via a push-pull switch motif. We show that the output signal quickly converges to the input one. Under ideal conditions, finite-time convergence would be achieved. We also show that the circuit gives a good approximation of the input signal derivative.

10:54-11:18 WeMo2T1.2

Efficient Learning in Metabolic Pathway Designs through Optimal Assembling (I), pp. 7-12

Carbonell, Pablo	University of Manchester
Fazulon, Jean-Loup	University of Manchester
Breitling, Rainer	University of Manchester

Engineering biology is a key enabling technology at the forefront of the new industrial bioeconomy. Rapid prototyping for bio-based 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

11:18-11:42 WeMo2T1.3

Multiobjective Optimization of Gene Circuits for Metabolic Engineering (I), pp. 13-16

Otero-Muras, Irene	IIM-CSIC
Mannan, Ahmad	University of Warwick
Banga, Julio R.	IIM-CSIC (Spanish Council for Scientific Research)
Oyarzún, Diego A.	University of Edinburgh

Metabolic engineering has enabled the production of a wealth of chemicals with microorganisms. Classic strategies for pathway engineering rely on the expression of heterologous enzymes in a host that convert native intermediates into target products. Although traditional implementations are based on open-loop control, recent advances in gene circuit engineering offer opportunities for building feedback systems that dynamically control pathway activity. Here we present a framework for the design of metabolic control circuits based on multiobjective optimization. We show that positive and negative feedback loops produce a range of optimal dynamics along a Pareto front. Such regulatory loops define connectivities between pathway intermediates and enzymatic genes that trade-off metabolic production against the burden to the host. Our results lay the groundwork for the automated design of gene circuitry in applications at the interface of synthetic biology and metabolic engineering.

11:42-12:06 WeMo2T1.4

Leveraging Resource Competition for Part Characterization in Cell-Free Extracts (I), pp. 17-23

Gyorgy, Andras — New York University Abu Dhabi

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 part 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.

WeMo2T2 — Salón de Actos Cubo Rojo (Red Cube's Events Room)

Computational Methods for Large-Scale Dynamic Modelling in Systems Medicine (Invited Session)

Chair: Weindl, Daniel — Helmholtz Zentrum München
Co-Chair: Villaverde, Alejandro F. — IIM-CSIC
Organizer: Villaverde, Alejandro F. — IIM-CSIC
Organizer: Hasenauer, Jan — University of Bonn

10:30-10:54 — WeMo2T2.1

Efficient Computation of Steady States in Large-Scale ODE Models of Biochemical Reaction Networks (I), pp. 32-37

Lines, Glenn Terje — Simula Research Laboratory
Paszkowski, Łukasz — Simula Research Laboratory
Schmiester, Leonard — Helmholtz Zentrum München
Weindl, Daniel — Helmholtz Zentrum München
Stapor, Paul — Helmholtz Zentrum München
Hasenauer, Jan — University of Bonn

In systems and computational biology, ordinary differential equations are used for the mechanistic modelling of biochemical networks. These models can easily have hundreds of states and parameters. Typically most parameters are unknown and estimated by fitting model output to observation. During parameter estimation the model needs to be solved repeatedly, sometimes millions of times. This can then be a computational bottleneck, and limits the employment of such models.

In many situation the experimental data provides information about the steady state of the biochemical reaction network. In such cases one only needs to obtain the equilibrium state for a given set of model parameters. In this paper we exploit this fact and solve the steady state problem directly rather than integrating the ODE forward in time until steady state is reached. We use Newton's method -- like some previous studies -- and develop several improvements to achieve robust convergence. To address the reliance of Newton's method on good initial guesses, we propose a continuation method. We show that the method works robustly in this setting and achieves a speed up of up to 100 compared to using ODE solves.

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
Chaouiya, 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 qualify such deviations.

11:18-11:42 — WeMo2T2.3

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

Villaverde, Alejandro F. — IIM-CSIC
Raimundez-Alvarez, Elba — Technische Universität München, Helmholtz Zentrum München
Hasenauer, Jan — University of Bonn
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
Trairatphisan, Panuwat — University Hospital Heidelberg
Gabor, Attila — MTA SZTAKI

Saez-Rodriguez, Julio RWTH Aachen

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 (PKN's) 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.

12:06-12:30 WeMo2T2.5

Challenges in the Calibration of Large-Scale Ordinary Differential Equation Models (I), pp. 58-64

Kapfer, Eva-Maria Technische Universität München, Center for Mathematics
Stapor, Paul Helmholtz Zentrum München
Hasenauer, Jan University of Bonn

Mathematical models based on ordinary differential equations have been employed with great success to study complex biological systems. With soaring data availability, more and more models of increasing size are being developed. When working with these large-scale models, several challenges arise, such as high computation times or poor identifiability of model parameters. In this work, we review and illustrate the most common challenges using a published model of cellular metabolism. We summarize currently available methods to deal with some of these challenges while focusing on reproducibility and reusability of models, efficient and robust model simulation and parameter estimation.

WeAf1T1 Auditorio Cubo Azul (Blue Cube's Auditorium)

Dynamics and Control of Biological Systems I (Regular Session)

Chair: Klamt, Steffen Max Planck Institute for Dynamics of Complex Technical Systems
Co-Chair: Fiore, Davide University of Naples Federico II

14:00-14:24 WeAf1T1.1

Disturbance Response Analysis of Cell-To-Cell Communication Systems Based on Spatial Frequency Decomposition, pp. 65-69

Kotsuka, Taishi Keio University
Hori, Yutaka Keio University

In biomolecular communication networks, bacterial cells communicate with each other using a cell-to-cell communication mechanism mediated by diffusible signaling molecules. The dynamics of molecular concentrations in such systems are approximately modeled by reaction-diffusion equations. In this paper, we analyse the ability of cell-to-cell communication systems to attenuate impulsive disturbances with various spatial frequency profiles by computing the integrated squared concentration of molecules. In particular, we perform in-depth study of disturbance responses for an activator-repressor-diffuser biocircuit in the spatial frequency domain to characterize its spatial frequency gain.

14:24-14:48 WeAf1T1.2

External and Multicellular Feedback Control of the Genetic Toggle-Switch for Cell Regulation and Applications in Synthetic Biology, pp. 70-71

Fiore, Davide University of Naples Federico II
di Bernardo, Mario University of Naples Federico II

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].

[1] Fiore, D., Guarino, A., and di Bernardo, M. (2019). Analysis and control of genetic toggle switches subject to periodic multi-input stimulation. IEEE Control Systems Letters, 3(2), 278-283.

[2] Guarino, A., Fiore, D., and di Bernardo, M. (2019). In-silico feedback control of a MIMO synthetic toggle switch via pulse-width modulation. In 2019 European Control Conference (ECC). [Preprint available at arXiv:1811.06263].

[3] Salzano, D., Fiore, D., and di Bernardo, M. (2019). Ratiometric control of cell populations endowed with synthetic toggle switches. Submitted to IEEE Conference on Decision and Control 2019. [Preprint available at arXiv:1903.09414].

14:48-15:12 WeAf1T1.3

Period - Control in a Coupled System of Two Genetic Oscillators for Synthetic Biology, pp. 72-77

Firippi, Eleni Université Côte d'Azur, Inria, INRA, CNRS, Sorbonne Université,
Chaves, Madalena INRIA

Biological complex mechanisms with oscillatory behavior are often modeled by high dimensional nonlinear ODEs systems, which makes the analysis and understanding 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.

15:12-15:36 WeAf1T1.4

Validation and External Feedback Control of a Molecular-Titration Module in Escherichia Coli Using Microfluidics, pp. 78-79

di Bernardo, Mario University of Naples Federico II
Shannon, Barbara Mary University of Bristol
Postiglione, Lorena TIGEM
Zamora Chimal, Criseida Gabriela University of Bristol
Annunziata, Fabio University of Bristol
Fiore, Gianfranco University of Bristol
Matyjaszkiewicz, Antoni University of Bristol
Grierson, Claire University of Bristol
Marucci, Lucia University of Bristol
Savery, Nigel University of Bristol

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).

15:36-16:00 WeAf1T1.5

Temperature-Dependent Dynamic Control of the TCA Cycle for Increased Volumetric Productivity of Itaconic Acid Production by Escherichia Coli, pp. 80-81

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 (pR) in strain ita36A. The expression of this promoter was controlled by the temperature-sensitive repres¬sor CI857 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 expensive inducers and has the potential to be generally used to improve cell factory performance.

WeAf1T2 Salón de Actos Cubo Rojo (Red Cube's Events Room)

Dynamics and Control of Biological Systems II (Regular Session)

Chair: Shoemaker, Jason — University of Pittsburgh

Co-Chair: Marucci, Lucia — University of Bristol

14:00-14:24 WeAf1T2.1

Robust Optimal Control-Based Design of Combined Chemo and Immunotherapy Delivery Profiles, pp. 82-87

Moussa, Kaouther — GIPSA-Lab

Fiacchini, Mirko — GIPSA-Lab, CNRS

Alamir, Mazen — Gipsa-Lab (CNRS-University of Grenoble)

This paper addresses the problem of drug injection schedules design for cancer treatment, in the presence of model parametric uncertainties. It is commonly known that achieving optimal recovery performances under uncertainties is a complex task. Therefore, we propose to use a recent optimal control approach, based on the moment optimization framework. This method allows to formulate and solve robust optimal control problems by taking into account uncertain parameters and initial states, modeled as probability distributions. We analyse a two dimensional model that describes the interaction dynamics between tumor and immune cells. We also explore potentially optimal ways to combine chemo- and immunotherapy treatments, assuming the knowledge of probability distributions of some uncertain model parameters, namely, the tumor growth rate and the rate of immune cells influx. Numerical simulations are carried out in order to illustrate the effects of parametric uncertainties on dynamics, when using a nominal injection profile. Finally, we compare the recovery performance of nominal and robust schedules.

14:24-14:48 WeAf1T2.2

Towards Automated Control of Embryonic Stem Cell Pluripotency, pp. 88-93

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.

14:48-15:12 WeAf1T2.3

Visual-Vestibular Compensation in Balance Recovery: A Function Transfer Model-Based Analysis, pp. 94-99

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 occurs 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 throughout successive stimulation sessions. The analysis of the feet centre-of-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.

15:12-15:36 WeAf1T2.4

Kinetic Modeling of Coagulation and Fibrinolysis, pp. 100-106

LeCover, Rachel — Cornell University

Orfeo, Thomas	Department of Biochemistry, College of Medicine, the University
Brummel-Ziedins, Kathleen	Department of Biochemistry, College of Medicine, the University
Bravo, Maria	Department of Biochemistry, College of Medicine, the University
Pusateri, Anthony	Army Institute of Surgical Research, Joint Base San Antonio Fort
Varner, Jeff	Cornell

Thromboelastic testing provides an assessment of a patient's coagulation and fibrinolytic systems. In recent years, thromboelastic testing has become an important point of care technique. However, its direct connection with the underlying biochemistry of coagulation and clot formation is not obvious. Toward this issue, we describe a validated reduced order mathematical model of coagulation and fibrinolysis, consisting of 22 ordinary differential equations, which described clot formation from initiation of the coagulation cascade through the degradation of polymerized fibrin by plasmin. We trained the model via leave one out cross validation on ROTEM measurements, a common thromboelastic test, on four patients, and then predicted ROTEM trajectories on four unseen patients, in whole blood and whole blood with the addition of 2 nM tissue plasminogen activator. Following model validation, sensitivity analysis suggested which biochemical interactions and species controlled the system response. Lastly, we investigated if we could estimate protein concentrations from commonly reported thromboelastic metrics. These estimation studies suggested we could (on average) relearn the initial fibrinogen concentration to within 20% of its true value. Taken together, this work presents a model which connects the underlying biochemistry of coagulation and clot formation in patients to a common point of care thrombelastographic test.

15:36-16:00 WeAf1T2.5

Strain-Specific Immune Response to Influenza Virus Infection, pp. 107-112

Ackerman, Emily	University of Pittsburgh
Mochan, Ericka	Carlow University
Shoemaker, Jason	University of Pittsburgh

A major question in influenza infection pathology is whether viruses of varying virulence invoke distinct immune responses. While efforts have attempted to mathematically characterize the host immune response to influenza virus infection, there has been no previous exploration of strain-specific infection dynamics. Here, a mechanism-based mathematical model is developed and used to compare the immune dynamics invoked by deadly H5N1 and moderately pathogenic H1N1 viruses. Results suggest that the kinetics of the immune response, specifically those related to the virus as well as those involved in interferon production, differ between H1N1 and H5N1 infections. The ability to predict strain differences could aid in clinical understanding of infection severity and take a step towards future application of patient-specific treatment profiles.

WeBrAfCP Hall Cubo Azul (Blue Cube's Hall)

Poster I + Coffee Th (Poster Session)

Chair: Vignoni, Alejandro	Universitat Politècnica De Valencia
Co-Chair: Boada, Yadira	Universitat Politècnica De València

16:00-17:00 WeBrAfCP.1

Identification of Heterogeneous Parameters in an Intracellular Reaction Network from Population Snapshot Measurements through Sensitivity Analysis and Neural Network, pp. 113-118

Lee, Dongheon	Texas A&M University
Jayaraman, Arul	Texas A&M Univ
Kwon, Joseph	UCLA

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 evaluations of the IPBM 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 online 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 WeBrAfCP.4

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 INRIA
Gouze, Jean-Luc INRIA
Baldazzi, 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 Desnoues 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 WeBrAfCP.5

A Multiscale Model of Defective Interfering Particle Replication During Influenza Virus Infection, pp. 131-132

Rüdiger, Daniel Max Planck Institute for Dynamics of Complex Technical Systems
Laske, Tanja Otto-Von-Guericke-Universität
Reichl, Udo Max Planck Institute for Dynamics of Complex TechnicalSystems

Defective interfering particles (DIPs) were proposed as antiviral agents due to their capability to potently impede influenza virus replication. Mathematical models have already been employed to analyze DIP-induced dynamics, however, these approaches focused either on the intra- or the extracellular level of virus infection. To investigate how DIP interference affects influenza virus infection and production in animal cell cultures, we implemented DIP kinetics in a recently published multiscale model of influenza virus replication that covers critical steps from virus genome replication to virus spread in a cell population. The new model developed describes well the inhibiting effects of DIPs on influenza infection dynamics for different experimental conditions.

16:00-17:00 WeBrAfCP.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 where 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 microalga Tisochrysis lutea and the transition from aerobic to anaerobic conditions in the yeast Saccharomyces cerevisiae.

16:00-17:00 WeBrAfCP.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.

16:00-17:00 WeBrAfCP.9

Fluorescence Calibration and Color Equivalence for Quantitative Synthetic Biology, pp. 143-148

Vignoni, Alejandro Universitat Politècnica De Valencia
Boada, Yadira Universitat Politècnica De València
Andreu-Vilarroig, Carlos Universitat Politècnica De València
Alarcón, Iván Universitat Politècnica De València
Boada Acosta, Lissette Anahí Universidad De Las Fuerzas Armadas ESPE
Requena Gutiérrez, Adrián Universitat Politècnica De València
Picó, Jesús Universitat Politecnica De Valencia

Synthetic Biology, the engineering of biology, is an evolving discipline. The complexity of the gene circuits being designed is increasing. And we are reaching the point where mathematical models are necessary and essential tools for the design of these gene circuits. Models can predict circuit behavior and guide the selection of suitable circuit components and implementations. However, it is necessary to perform parameter estimation in order to use these models correctly. Measurement calibration, and in particular, fluorescence and absorbance calibrations, is essential for the reproducibility of biological experiments. Moreover, the use of calibrated measurements increases dramatically the usability and interpretability of models and parameters estimated with them. Here, we report a set of protocols and calibration procedures allowing us to obtain measurements of fluorescent E. coli cells in Molecules of Equivalent Fluorescein (MEFL) per cell for GFP constructs and Molecules of Equivalent Fluorophore for other proteins such as YFP, sfGFP, and RFP. These simple, low-cost unit calibration protocols can be used to produce units and comparable models, improving dramatically the usability of these models for modular construction of genetic circuits in synthetic biology.

Program and Abstracts Thursday October 17

Track T1	Track T2
09:00-10:00 ThMo1P Auditorio Cubo Azul (Blue Cube's Auditorium) Computational Modeling of Whole-Body Metabolism Permits Novel Insight into Host-Microbiome Co-Metabolism. Ines Thiele, National University of Ireland, Galway	
10:00-10:30 ThBrMoC, Hall Cubo Azul (Blue Cube's Hall), Coffee Break Th	
10:30-12:30 ThMo2T1 Auditorio Cubo Azul (Blue Cube's Auditorium) Design and Control of Synthetic Biological Systems and Circuits	10:30-12:30 ThMo2T2 Salón de Actos Cubo Rojo (Red Cube's Events Room) Bioreactor Modelling, Supervision and Control
12:30-14:00 ThNLu, Hall Cubo Azul (Blue Cube's Hall), Lunch Th	
14:00-16:00 ThAf1T1 Auditorio Cubo Azul (Blue Cube's Auditorium) Modelling of Complex Biological Systems I	14:00-16:00 ThAf1T2 Salón de Actos Cubo Rojo (Red Cube's Events Room) Modelling of Complex Biological Systems II
16:00-17:00 ThBrAfCP Hall Cubo Azul (Blue Cube's Hall) Poster II + Coffee Th	
17:00-17:45 ThAf2P Auditorio Cubo Azul (Blue Cube's Auditorium) 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	
18:15-22:15 ThAf2Di, Nou Raco Restaurant Conference Dinner	

Technical Program for Thursday October 17, 2019

ThMo2T1	Auditorio Cubo Azul (Blue Cube's Auditorium)
Design and Control of Synthetic Biological Systems and Circuits (Regular Session)	
Chair: Carbonell, Pablo	University of Manchester
Co-Chair: Gyorgy, Andras	New York University Abu Dhabi

10:30-10:54 ThMo2T1.1

A Method for Design of Expression Tracking Controllers for Gene Regulatory Networks, pp. 149-156

Mori, Yoshihiro — Kyoto Institute of Technology
Kuroe, Yasuaki — Kyoto Institute of Technology
Ingalls, Brian P. — Univ of Waterloo

As the synthetic biology community continues to refine experimental techniques for construction of gene regulatory networks, there is continued need for computational design tools to efficiently achieve desired performance. Tracking controllers play a fundamental role in a range of control engineering tasks. In this paper we address the design of expression tracking controllers for gene regulatory networks. We employ a class of simple networks as controllers and describe gene expression dynamics via a piecewise affine approximation of general nonlinear model formulations. We propose a method for the design of tracking controllers. In the case of regulation of the activity of a single gene, we derive an analytic description of a parameterization of tracking controllers. The results are illustrated with numerical examples.

10:54-11:18 ThMo2T1.2

Automated Design of Bio-Switches for Synthetic Biology: The Role of Molecular Noise, pp. 157-158

Carlos Xose, Sequeiros-Ferreiro — University of Vigo
Vázquez Cendón, Carlos — Universidade Da Coruña
Banga, Julio R. — IIM-CSIC (Spanish Council for Scientific Research)
Otero-Muras, Irene — IIM-CSIC

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 ecient 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.

11:18-11:42 ThMo2T1.3

Global Stabilization of a Genetic Positive Feedback Loop Via the Design of a Synthetic Auto-Repression, pp. 159-164

Chambon, Lucie — INRIA
Gouze, Jean-Luc — INRIA

Genetic positive feedback loops are essential for cell differentiation processes. They are accurately modeled with N-dimensional non-linear 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.

11:42-12:06 ThMo2T1.4

Exploiting Ultrasensitivity for Biomolecular Implementation of a Control System without Error Detection, pp. 165-171

Montefusco, Francesco — University of Padova
BULAI, Iulia Martina — Departement of Information Engineering, University of Padova, Vi

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.

12:06-12:30 ThMo2T1.5

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

Nóbel Santos-Navarro, Fernando	Universitat Politecnica De Valencia
De Battista, Hernán	Universidad Nacional De La Plata - CONICET
Nuñez, Sebastián	Universidad Nacional De La Plata - CONICET
Picó, Jesús	Universitat Politecnica De Valencia

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 either large excursions in the desired set-point or limitations caused by an increased metabolic burden in the cell.

ThMo2T2 Salón de Actos Cubo Rojo (Red Cube's Events Room)

Bioreactor Modelling, Supervision and Control (Invited Session)

Chair: Bar, Nadav S.	Norwegian Univ of Science and Technology
Co-Chair: Mairet, Francis	Ifremer
Organizer: Bernard, Olivier	INRIA
Organizer: Bar, Nadav S.	Norwegian Univ of Science and Technology

10:30-10:54 ThMo2T2.1

About Overyielding with Mixed Cultures in Batch Processes (I), pp. 179-184

Harmand, Jérome	INRA
Rapaport, Alain	INRA
NIDELET, Thibault	INRA

This paper investigates - via modeling - several possible explanations of overyielding observed in mixed cultures cultivated in batch reactors. It is rst 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.

10:54-11:18 ThMo2T2.2

FBA-Based Simulator of Saccharomyces Cerevisiae Fed-Batch Cultures Involving an Internal Unbalanced Metabolite, pp. 185-190

Plaza, José	Université Libre De Bruxelles, 3BIO-BioControl
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 cost 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.

11:18-11:42 ThMo2T2.3

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 operational 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.

11:42-12:06 ThMo2T2.4

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
Daume, 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 parametrization 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

Modeling Bounded Random Fluctuations in Biological Systems: Application to the Chemostat Model with Two Species (I), 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 Ornstein-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 Auditorio Cubo Azul (Blue Cube's Auditorium)

Modelling of Complex Biological Systems I (Regular Session)

Chair: Bernaerts, Kristel — University of Leuven (KU Leuven)

Co-Chair: Balsa-Canto, Eva — CSIC

14:00-14:24 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.

[1] Schneider P., Klamt S. (2019) Bioinformatics, in press.

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 - University of Minho
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

Saldida, 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
Milias-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 (ΔrG) and concentrations (c) are estimated by variability analysis. As the space of v, ΔrG 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 ΔrG 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 stoichometric 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 caused 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 networks 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.

ThAf1T2 Salón de Actos Cubo Rojo (Red Cube's Events Room)

Modelling of Complex Biological Systems II (Regular Session)

Chair: di Bernardo, Diego	TIGEM
Co-Chair: Waldherr, Steffen	KU Leuven

14:00-14:24 ThAf1T2.1

Dirac Mixture Distributions for the Approximation of Mixed Effects Models, pp. 223-229

Wang, Dantong	Helmholtz Zentrum, Muenchen
Stapor, Paul	Helmholtz 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 mixture distributions obtained using Monte-Carlo, quasi Monte-Carlo, and sigma point methods. Here, we propose the use of a method based on the Cramér-von Mises Distance, which has been introduced in the context of filtering. We assess the accuracy of the different methods using several problems and provide the first scalability study for the Cramér-von Mises Distance method. Our results indicate that for a given number of points, the method based on the modified Cramér-von Mises Distance method tends to achieve a better approximation accuracy than Monte-Carlo and quasi Monte-Carlo methods. In contrast to sigma-point methods, the method based on the modified Cramér-von Mises Distance allows for a flexible number of points and a more accurate approximation for nonlinear 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 Stuttgar
Allgower, 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.

14:48-15:12 ThAf1T2.3

TFEB Dynamical Model Reveals a Novel Feedback Loop Biological Mechanism, pp. 236-241

Napolitano, Sara — University of Naples Federico II
Ruolo, Iacopo — University of Naples Federico II
Perrino, Giansimone — Telethon Institute of Genetics and Medicine
di Bernardo, Diego — TIGEM

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 drivingTFEB regulation mediated by autophagy.

15:12-15:36 ThAf1T2.4

Population Balance Modeling of Activated Sludge Microcolony Growth and Breakage, pp. 242-243

Totis, Niccolo — KU Leuven
Christiaens, an-sofie — KU Leuven
Smets, Ilse — KU Leuven, Department of Chemical Engineering, CREaS
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 by 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 ThAf1T2.5

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.

ThBrAfCP Hall Cubo Azul (Blue Cube's Hall)

Poster II + Coffee Th (Poster Session)

Chair: Boada, Yadira — Universitat Politècnica De València
Co-Chair: Vignoni, Alejandro — Universitat Politècnica De Valencia

16:00-17:00 ThBrAfCP.1

Extended Kalman Filter for Biomass Estimation Using Combined Frequent and Infrequent Measurements with Stochastic Model, pp. 250-251

Tuveri, Andrea — Norwegian University of Science and Technology
Lira Parada, Pedro Antonio — Norwegian University of Science and Technology
Pérez-García, Fernando — NTNU
Bar, Nadav S. — Norwegian Univ of Science and Technology

Microbial biocatalytic processes are non-linear multiple input multiple output systems, and the application of estimators to acquire information of the states is beneficial for bioprocess development. In the present study, we apply a continuous-discrete Extended Kalman Filter for biomass estimations, in a system governed by stochastic differential equations. The aim is to obtain reliable values of on-line signals with in-situ near-infrared spectroscopy through correction with the less frequent off-line measurements. We will later use the estimated signals for implementing feedback control actions in a real Corynebacterium glutamicum fermentation process. This approach allows the use of on-line and off-line data to update parameters and process noise for ensuring a more robust estimation.

16:00-17:00 ThBrAfCP.2

Evaluating the Performance of a Post-Translational Dynamic Metabolic Control System, pp. 252-257

Euler, Christian — University of Toronto
Kadam, Kaustubh — University of Toronto
Mahadevan, Radhakrishnan — University of Toronto

Dynamic control is a common approach to solve the tradeoff between productivity and yield that exists in engineered microbial metabolisms. Here we explore the possibility of implementing a dynamic control strategy based on direct activity modulation of a hypothetical optogenetic enzyme. With this system we sought to understand whether such a strategy is practical for controlling flux partitioning between biomass and production pathways, and whether it could be used to explore the effect of switching time on the performance of dynamic control strategies. We find that, while a protein-level control system is likely feasible in a model metabolism, several barriers to implementation and performance exist. Based on these limitations we suggest that careful balancing of protein expression at the biomass-production split node is required to implement such a system.

16:00-17:00 ThBrAfCP.3

Characterising Relationships between Model Parameters for Context-Aware Biocircuit Design (I), pp. 258-259

Grozinger, Lewis — School of Computing, Newcastle University
Goni-Moreno, Angel — School of Computing, Newcastle University

Mathematical models are essential for the design of predictable biological circuits. These circuits are not closed systems and the physiology of the host organism can have significant impact on behaviour through host-circuit interactions. Such interactions, and the environment, provide a context in which the circuit operates. Models accounting for context are fundamental to achieving the design of novel biological circuits that are reliable, robust and generalisable.

Models of biocircuits integrating context often formulate a coarse-grained description of host-circuit interactions to maintain the tractability of the model. We propose to build upon these approaches by inferring contextual information from qualitative

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 cover more of the design space and allow 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 ThBrAfCP.4

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

Lira Parada, Pedro Antonio	Norwegian University of Science and Technology
Pettersen, Even	Norwegian University of Science and Technology
Pérez-García, Fernando	NTNU
Bar, Nadav S.	Norwegian Univ of Science and Technology

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 ThBrAfCP.5

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

Schade, Sophia	Alacris Theranostics GmbH
Muradyan, Artur	Alacris Theranostics GmbH
Kessler, Thomas	Alacris Theranostics GmbH
Lange, Bodo	Alacris Theranostics GmbH
Wierling, Christoph	Alacris Theranostics GmbH

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 qualitatively 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 ThBrAfCP.6

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

Vysma, Morris	University of Newcastle
Welsh, James	University of Newcastle
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 malregulation 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 ThBrAfCP.7

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

Alvarez Villanueva, Patricia	I2SysBio University of Valencia-CSIC
Corbín, Paola	I2SysBio University of Valencia-CSIC
Ruiz, Mario	I2SysBio University of Valencia-CSIC
Peretó, Juli	I2SysBio University of Valencia-CSIC
Tortajada, Marta	ADM-Biopolis

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 ThBrAfCP.8

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

Guarino, Agostino	Universita' Degli Studi Di Napoli "Federico II"
Shannon, Barbara Mary	University of Bristol
Marucci, Lucia	University of Bristol
Grierson, Claire	University of Bristol
Savery, Nigel	University of Bristol
di Bernardo, Mario	University of Naples Federico II

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 ThBrAfCP.9

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

Reynoso-Meza, Gilberto	Pontificia Universidade Católica

	De Paraná
Vignoni, Alejandro	Universitat Politècnica De Valencia
Boada, Yadira	Universitat Politècnica De València
Picó, Jesús	Universitat Politecnica De Valencia
Pico-Marco, Enric	Technical University of Valencia

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.

16:00-17:00 ThBrAfCP.10

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

Marie-Joelle, VIROLLE	Institute for Integrative Biology of the Cell (I2BC), CEA, CNRS,
Millan-Oropeza, Aaron	Institut National De La Recherche Agronomique (INRA)
Henry, Celine	Institut National De La Recherche Agronomique (INRA)
Lejeune, Clara	Université Paris-Saclay
David, Michelle	Université Paris-Saclay

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.

Program and Abstracts Friday October 18

Track T1	Track T2
09:00-09:45 FrMo1P Auditorio Cubo Azul (Blue Cube's Auditorium) Keynote 3. Understanding Biological Function in the Context of Biological Heterogeneity. Alexander Hoffmann, Institute for Quantitative and Computational Biosciences, UCLA	
09:45-10:15 FrBrMoC, Hall Cubo Azul (Blue Cube's Hall), Coffee Break Fr	
10:15-11:51 FrMo2T1 Auditorio Cubo Azul (Blue Cube's Auditorium) Network Inference and Modelling	10:15-11:51 FrMo2T2 Salón de Actos Cubo Rojo (Red Cube's Events Room) Control and Optimisation of Microalgae
12:00-13:00 FrNP Auditorio Cubo Azul (Blue Cube's Auditorium) 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	
13:00-14:00 FrAfCo, Hall Cubo Azul (Blue Cube's Hall) Farewell Cocktail	

Technical Program for Friday October 18, 2019

FrMo2T1 Auditorio Cubo Azul (Blue Cube's Auditorium)

Network Inference and Modelling (Regular Session)

Chair: Bogaerts, Philippe — Université Libre De Bruxelles
Co-Chair: Braniff, Nate — University of Waterloo

10:15-10:39 FrMo2T1.1

Optimal Experimental Design for a Bistable Gene Regulatory Network, pp. 289-295

Braniff, Nate — University of Waterloo
Richards, Addison — University of Waterloo
Ingalls, Brian P. — Univ of Waterloo

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 across the monostable and bistable regimes. We use the linear noise approximation for the local error model and apply logistic regression to capture the switching probabilities between the stable equilibria. We then use this Fisher information matrix to generate locally optimal experimental designs for this system. This leads to a simple, qualitative approach to optimal experimental design based on experimental detection of bimodality.

10:39-11:03 FrMo2T1.2

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 presumptions 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.

11:03-11:27 FrMo2T1.3

A Geometric Approach to Target Identification, pp. 303-304

Wang, Yu — KTH Royal Institute of Technology
Jacobsen, Elling — KTH Royal Institute of Technology

Inferring the direct gene or protein targets of external perturbations is a key problem in drug discovery. In this work, we consider target identification based on time-series data obtained after perturbing the cell with the compound of interest (COI). In contrast to previous work in this area, we do not rely on fitting a full network model to recover the target. Rather, we take a geometric perspective on the target identification problem and show that, by considering the span of individual gene response vectors in the sample space, it is possible to identify targets with high confidence even if the experimental data are not informative for inferring other parts of the network. Moreover, individual targets can be identified independently. The proposed method can also be used to analyze the information content in the available data with respect to the identifiability of individual genes as targets. We demonstrate the results on a 20 gene network. We show that a target can be identified from a single time-series experiment using significantly fewer samples than there are nodes in the network.

11:27-11:51 FrMo2T1.4

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

Mathematical models of metabolic networks are often underdetermined systems with more unknown fluxes than available equality constraints describing mass balances and external flux

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	Université De Mons
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 concentration without biomass input, which leads to a monomorphic population. The second case, considering a biomass input without substrate, leads to quota heterogeneity. Simulations are then carried out for the two case studies (showing good agreements with the analytical solutions) and for a more general case. Finally, we show that the error induced by the average quota approach increases considerably with microalgae plasticity (i.e. the maximal over minimal quota ratio), which points out the benefit of considering quota heterogeneity in these cases.

10:39-11:03 FrMo2T2.2

Extremum-Seeking for Micro-Algae Biomass Productivity Maximization: An Experimental Validation (I), pp. 317-322

Feudjio Letchindjio, Christian Gabin	University of Mons
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 textit{Dunaliella tertiolecta} 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.

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.

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Session Chair	C
Session Co-chair	CC

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Maps

Universitat Politècnica de València (UPV)

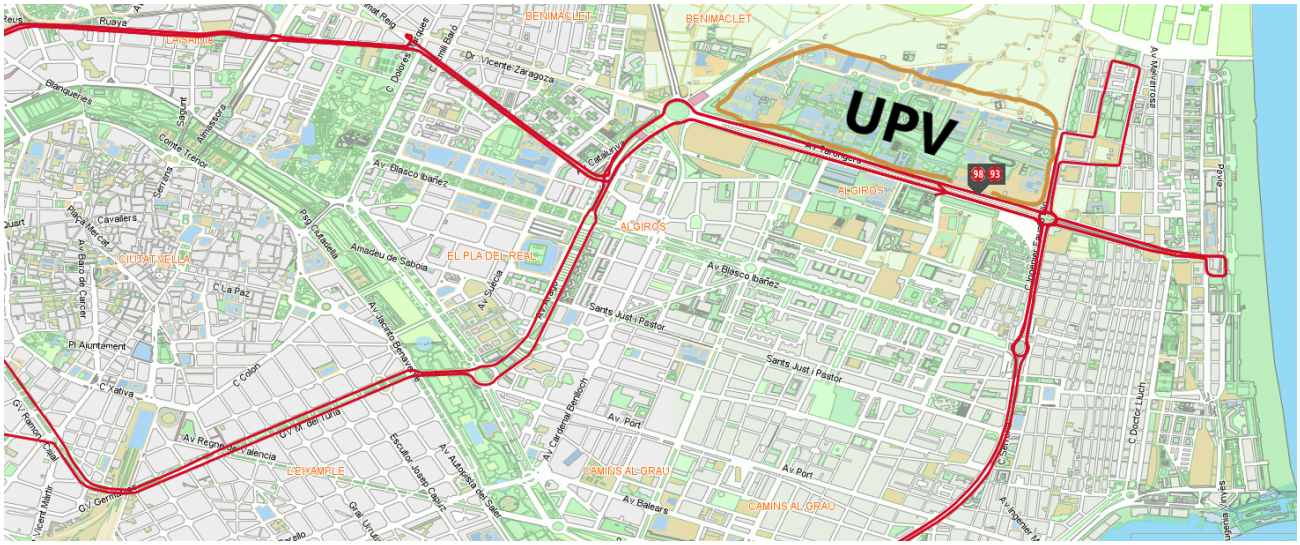
CPI Building (8B). Hall Cubo Azul (Blue Cube's Hall)

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 Valéncia 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.