International Federation of Automatic Control

Program Booklet

FOSBE 2024

10th IFAC Conference on Foundations of Systems Biology in Engineering

Corfu Island, Greece, September 8-11 2024

Edited by

Maria I. Klapa, FORTH/ICE-HT, Greece
Kristel Bernaerts, KU Leuven, Belgium
Alejandro Vignoni, Universitat Politècnica de València, Spain

Program at a Glance

Sunday September 8, 2024

14:30-15:00 SuAT1 Room NAFSIKA **Opening Remarks** *Maria I. Klapa*, FORTH/ICE-HT, Greece
15:00-16:00 SuBT1 Room NAFSIKA **Keynote Lecture I** **Microbiome data science: from earth microbiome to global virome** *Nikos Kyrpides*, DOE Joint Genome Institute, Lawrence Berkeley National Laboratory, USA
16:00-17:10 SuCT1 Room NAFSIKA **General Session 1** – **Modeling Microbial Systems** *Session Chair: Kristel Bernaerts, KU Leuven, Belgium*
17:10-17:40 Coffee Break
17:40-18:30 SuDT1 Room NAFSIKA **General Session 1** – **Modeling Microbial Systems** *Session Chair: Kristel Bernaerts, KU Leuven, Belgium*
18:30-19:00 SuET1 Room NAFSIKA **Invited Lecture 3** – **Taming the Genomic Era and Democratising Bioinformatics to Face Biodiversity Challenges** *Tereza Manousaki, HCMR, Greece*
19:00-20:00 SuFT1 Room NAFSIKA **FOSBE AWARD PRESENTATION** ***Chairs:*** *Maria I. Klapa, FORTH/ICE-HT, Greece;* *Alejandro Vignoni, Universitat Politécnica de València, Spain* **Synthetic Biology and Biosystems Control** Jesus Pico, Universitat Politécnica de València, Spain
20:30-23:00 SuGT1 Veranda PERGOLA **Welcome Reception**

Monday September 9, 2024

09:00-10:50 MoAT1 Room NAFSIKA **General Session 2** – **Synthetic Biology** *Session Chair: Alejandro Vignoni*
10:50-11:10 Coffee Break
11:10-12:10 MoBT1 Room NAFSIKA **Panel Discussion 1** – **Systems & Synthetic Biology: Innovation & Entrepreneurship** *(Moderator: Livija Deban, Prokarium, UK)* **Panelists:**

Alejandro Vignoni, Technical University of Valencia, Spain *Nikos Kyrpides, DOE JGI, Lawrence Berkeley National Lab, USA* *Marc Biarnes Carrera, Prokarium, UK* *Traci Haddock, Asimov Inc., USA* *Massimo Lai, Astrazeneca, USA* *Spyros Vernardis, Eliptica Limited, UK*
12:30-17:30 **Excursion in the Island by bus including Lunch**
18:00-18:45 MoCT1 Room NAFSIKA **FRONTIERS IN SYSTEMS BIOLOGY YOUNG INVESTIGATOR AWARD ASSOCIATED WITH FOSBE 2024** **Chair:** Maria I. Klapa, FORTH/ICE-HT, Greece **Frontiers in Systems Biology: Breaking Down Silos and Integrating Datasets, Toolsets, and Mindsets in Partnership with FOSBE | Inauguration of the Young Investigator Award** *Yoram Vodovotz*, Field Chief Editor & *Thomas C. Collin*, Journal Manager **AWARD PRESENTATION:Computational Inference of Chemokine-Mediated Roles for the Vagus Nerve in Modulating Intra- and Inter-Tissue Inflammation** *Ashti Shah*, School of Medicine, University of Pittsburgh, USA
18:45-19:30 MoDT1 Room NAFSIKA **POSTER SESSION I - Pitches** *Chair: Spyridon (Spyros) Aleiferis, Complexity Cybernetics SPPC, Greece*
19:30-21:00 MoET1 Room CALYPSO **POSTER SESSION I - Presentations + Wine & Cheese Buffet**

Tuesday September 10, 2024

09:00-11:10 TuAT1 Room NAFSIKA **General Session 3 – Methods and Tools** *Session Chair: Steffen Waldherr, University of Vienna, Austria*
11:10-11:30 Coffee Break
11:30-12:30 TuBT1 Room NAFSIKA **Panel Discussion 2 – Systems & Synthetic Biology: What about training, funding and publishing?** *(Moderator: Maria I. Klapa, FORTH/ICE-HT, Greece)* **Panelists:** *John Hancock, Co-leader of ELIXIR Systems Biology Community, U. of Ljubljana, Slovenia* *Jesus Pico, IFAC TC 8.4 Leader, Technical University of Valencia, Spain* *Ioannis (Yannis) Androulakis, Rutgers University, USA* *Thomas C. Collin, Frontiers in Systems Biology* *Ashti Shah, School of Medicine, University of Pittsburgh, USA*
12:30-13:15 TuCT1 Room NAFSIKA **POSTER SESSION II - Pitches** *Chair: Yadira Boada, Universitat Politécnica de València, Spain*
13:15-15:00 TuDT1 Room CALYPSO (Presentations) + Veranda PERGOLA (Buffet)

POSTER SESSION II - Presentations + Light Lunch Buffet
15:00-16:20 TuET1 Room NAFSIKA **General Session 4** – **Control in Biology** *Session Chair: Jesus Pico, Universitat Politécnica de València, Spain*
16:20-17:00 Coffee Break
17:00-18:00 TuFT1 Room NAFSIKA **General Session 4** – **Control in Biology** *Session Chair: Jesus Pico, Universitat Politécnica de València, Spain*
18:00-19:00 TuGT1 Room NAFSIKA **Keynote Lecture II** *Session Chair: John Hancock, U. of Ljubljana, Slovenia* **Two Decades of BioModels: Promoting FAIR Sharing and Reproducibility of Computational Models in the Life Sciences** *Sheriff Malik Rahuman, European Bioinformatics Institute (EBI), UK*
19:30-23:00 **Guided Tour of the Old Town of Corfu (Unesco Monument) + Gala Dinner in Corfu town**

Wednesday September 11, 2024

09:00-10:30 WeAT1 Room NAFSIKA **General Session 5** – **Systems biology for Health** *Session Chair: Yannis Androulakis, Rutgers University, USA*
10:30-11:00 Coffee Break
11:00-11:30 WeBT1 Room NAFSIKA **General Session 5** – **Systems biology for Health** *Session Chair: Yannis Androulakis, Rutgers University, USA*
11:30-12:30 WeCT1 Room NAFSIKA **Award Ceremony & Closing Remarks** *Chairs: Maria I. Klapa, FORTH/ICE-HT, Greece; Kristel Bernaerts, KU Leuven, Belgium; Alejandro Vignoni, Technical University of Valencia, Spain*

IFAC INTERNATIONAL FEDERATION OF AUTOMATIC CONTROL

FOSBE 2024 Corfu Island, Greece • September 8 - 11

Table of Contents

Welcome Message

It is with great pleasure that we welcome you to the 10th IFAC International Conference on Foundations of Systems Biology in Engineering (FOSBE 2024) held on September 8-11, 2024, at the Divani Corfu Palace Hotel on the picturesque Corfu Island in Greece. The Conference is organized by the International Federation of Automatic Control (IFAC), supported by the Comité Español de Automática (CEA) acting as IFAC National Member Organization, in collaboration with the Institute of Chemical Engineering Sciences (ICE-HT) of the Foundation for Research & Technology - Hellas (FORTH), which leads the national organizing committee (NOC) in Greece. The Conference is co-sponsored by the European Infrastructure on Biological Data Management & Analysis, ELIXIR, with special support by its Systems Biology Community and the Greek Node (ELIXIR-GR). With more than 90 participants from academia, industry and scientific journals from 18 countries, of whom more than half are graduate students and post-doctoral fellows, the 2024 conference continues the mission of the FOSBE series to advance the fields of systems and synthetic biology through the integration of systems engineering, mathematical modeling, and process control principles, featuring a dynamic and interdisciplinary scientific program.

More specifically, FOSBE2024 comprises five sessions, two keynote and nine invited lectures, 19 solicited oral and 46 poster presentations, underscoring the remarkable progress in both systems and synthetic biology, driven by cutting-edge computational methodologies, including big data analysis and machine learning. All solicited contributions have been selected by the International Program Committee (IPC) through a rigorous review process. The conference is expected to provide a vital forum where researchers, industry leaders, and innovators from various countries and research & entrepreneurial environments come together to share innovative research and exploring new methodologies that are shaping the future of the field.

FOSBE 2024 also includes two panels: (1) "Systems & Synthetic Biology: Innovation & Entrepreneurship", and (2) "Systems & Synthetic Biology: What about training, funding and publishing?". The first panel is expected to initiate the discussion about the need for systems and synthetic biology research to move from the lab-scale to large-scale application and industrial solutions and products, combining the perspective of research experts, entrepreneurs and industry leaders. In the second panel, discussions are to focus on how best to educate the next generation of researchers equipped to excel in this multidisciplinary environment. Furthermore, the importance of fostering international collaboration and the challenges of securing funding to support both fundamental and applied research are to be also discussed. In addition, FOSBE 2024 aims to address broader challenges, such as the processes of editing, reviewing, and publishing in systems and synthetic biology. These discussions are to be greatly enriched by the participation of editors from leading journals, to provide nsights into the evolving landscape of scientific publishing in these fields. We underline the support of Frontiers in Systems Biology journal, which organizes a special session on "Breaking Down Silos and Integrating Datasets, Toolsets, and Mindsets in Partnership with FOSBE", inaugurating its Young Investigator Award.

FOSBE 2024 social program offers a rich cultural experience, beginning on Monday with a scenic tour through the lush Corfiot countryside visiting a koum-kouat distillery, learning about the process of making a traditional Corfiot liqueur, enjoying the local cuisine and panoramic views from the village of Lakones, and exploring the charming streets of Makrades before

returning to Corfu Town. On Tuesday, the program includes a guided walking tour of Corfu Town's historic sites, such as the Old Venetian Fortress, the Royal Palace of St. George & St. Michael, and the Church of Saint Spiridon, followed by a Gala Dinner at the Corfu Sailing Club, providing a perfect blend of culture, history, and networking opportunities. We encourage all participants to take time to explore the island of Corfu, known for its rich history, stunning landscapes, and vibrant culture. Whether you're strolling through the narrow streets of Corfu Town, a UNESCO World Heritage Site, enjoying the serene beaches, or sampling the local cuisine, we are confident that you will find Corfu to be as inspiring as the conference itself. Please do not hesitate to stop by the conference registration desk or reach out to any of our volunteers if you have questions or need assistance.

Finally, we would like to express our gratitute to everyone who contributed to the organization of FOSBE 2024. The event was made possible through the dedication and hard work of the National Organizing Committee (NOC), International Program Committee (IPC), area and session chairs, reviewers, and numerous volunteers. We also thankfully acknowledge the crucial role of our sponsors' generous support. Finally, we express our sincere appreciation to IFAC and FORTH/ICE-HT for their steadfast support, with a special reference to the Conference Manager, Mrs Angeliki Kosmatou, whose dedication, hard work and experience has substantially helped many times in the organization process.

We wish you a fruitful & rewarding meeting, sincerely hoping that you will enjoy your time at the conference and in Corfu, making FOSBE2024 a memorable and inspiring experience!

Maria Klapa (NOC chair), on behalf of the NOC

Kristel Bernaerts (IPC chair) and **Alejandro Vignoni** (IPC Co-chair), on behalf of the IPC

Committees

National Organizing Committee (NOC)

Chair: *Dr. Maria I. Klapa, FORTH/ICE-HT, GR*
Co-chair: *Prof. Dr. Demosthenis Sarigiannis, AUTh & NHRF*

NOC members

Angeliki Kosmatou (Conference Chair)
Irene Ioannidou (Logo Developer and Website Manager)

International Program Committee (IPC)

Chair: *Prof. Dr.* Kristel Bernaerts*. KU Leuven, BE*
Co-chair: *Prof. Dr. Alejandro Vignoni, Universitat Politécnica de València, ES*
Vice-chair from industry: Livija Deban, *Chief Scientific Officer, Prokarium, UK*

Androulakis Ioannis (Yannis), US
Balsa-Canto Eva, ES
Banga Julio, ES
Bar Nadav, NO
Batt Gregory, FR
Bernard Olivier, FR
Braatz Richard, US
Bruggeman Frank, NL
Chatziioannou Aristotelis, GR
Cho Kwang-Hyun, KR
de Jong Hidde, FR
di Bernardo Diego, IT
Doyle Frank, US
Findeisen Rolf, DE
Giordano Giulia, IT
Goñi-Moreno Ángel, ES
Gunawan Rudi, US
Hahn Jürgen, US
Hatzimanikatis Vassily, CH
Hori Yutaka, JP
Ingalls Brian, CA
Klipp Edda, DE
Kremling Andreas Kremling, DE
Macía Javier, ES
Mahadevan Radhakrishnan, CA
Maranas Costas, US
Ouzounis Christos, GR
Oyarzun Diego, UK
Picó Jesús, ES
Rocha Miguel, PT
Steuer Ralf, DE
Theodoropoulos Konstantinos (Kostas), UK
Vera Julio, DE
Waldherr Steffen, AU

Sponsors

International Federation of Automatic Control (IFAC)
- Biosystems and Bioprocesses, TC 8.4.

Co-Sponsored by

International Federation of Automatic Control (IFAC)
- TC 8.1. Control in Agriculture
- TC 8.2. Biological and Medical Systems
- TC 8.3. Modelling and Control of Environmental Systems

Comité Español de Automatica – CEA / IFAC National Member Organization

European Life Sciences Infrastructure ELIXIR
- Systems Biology Community
- Greek Node (ELIXIR-GR)

Computer Aids for Chemical Engineering (CACHE)

Financially Supported by

Gold Support Level

Institute of Chemical Engineering Sciences,
Foundation for Research & Technology Hellas (FORTH/ICE-HT), GR

Silver Support Level

Frontiers in Systems Biology

Bronze Support Level

Prokarium

General Support Level

Spanoudakis Konstantinos - ChemiC.S, GR

AstraZeneca, UK

ASIMOV, USA

Complexity Cybernetics, GR

ATHAL, GR

Registration, Social Program, Announcements

Registration Sunday September 8 – Tuesday September 10 2024

Sunday 8/9, 12.00 – 18.00
Monday 9/9, 8:45 – 12:30
Tuesday 10/9, 8:45 – 13:00

The registration desk is located in the reception area of the hotel. rs. The Conference Manager, Mrs. Angeliki Kosmatou (*kosmatou@iceht.forth.gr*) will be available to assist you. Please confirm your participation to the social events at the time of registration.

Conference website link

The conference website link is https://fosbe2024.iceht.forth.gr. You may directly access it through the following QR code.

Main Conference Room NAFSIKA & Poster Presentation Room CALYPSO

All sessions of the conference including the poster presentation pitches will take place in the main conference room of the Divani Corfu Palace hotel on the left side of the main hotel entrance (down the stairs). Posters will be mounted in stands located in the room CALYPSO, which is located next to the hotel reception on the ground floor.

Welcome Reception, Sunday September 8 2024, 20:30 – 23:00

The welcome reception will take place at the Veranda PERGOLA of the Divani Corfu Palace Hotel. This is located in the first floor of the hotel next to the main restaurant room.

Excursion in the Island by bus including Lunch, Monday September 9 2024, 12:30 – 17:30

The buses will leave from the Divani Corfu Palace Hotel lobby at 12:30PM sharp. Please be there by 12:20PM. For more details about the excursion, you may check the social program link at the conference website. Any further details about the buses will be provided by the organizers in due time.

Guided Tour of the Old Down of Corfu + Gala Dinner at the Corfu Sailing Club Restaurant, Tuesday September 10, 19:30 – 23:30

The buses will leave from the Divani Corfu Palace Hotel lobby at 19:30 sharp. Please be there by 19:20PM. For more details about this social event, you may check the social program link at the conference website.

Wireless Network

Please connect to the wireless network FOSBE2024 of the hotel. Further connection details will be provided at the registration desk.

Group Photo

The group photo will be taken in the morning coffee break of Tuesday, September 10 (11:10AM). The location of the group photo will be announced during the conference.

Instructions for Presenters, Session Chairs, Posters

Oral Presentations

The allocated time for the talks are as follows:

Type	Presentation time	Discussion time
Plenary	46 minutes	7 minutes
Invited	25 minutes	5 minutes
Regular	16 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 the main session room (NAFSIKA). 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 or post-doc will be given during the closing session, consisting of a certificate and a 100 Euros stipend. Frontiers in Systems Biology offers the possibility for the awardee to serve as topic coordinator in one of the two topics of the journal associated with FOSBE2024 with a certificate of recognition given to the young investigator upon completion by Frontiers.

Poster Presentations

The poster sessions take place in the CALYPSO room (next to the hotel reception). The poster size is at maximum 800 mm (W) x 1000 mm (H), portrait orientation. Posters may be put up on Sunday September 8 after 1PM and stay mounted until the end of the day on Tuesday September 10. The boards will be removed from the hotel space on Wednesday morning and any posters that have stayed mounted will be discarded. Board pins and tape will be available on-site. There will be a list with the allocated poster slot. Authors should also prepare 1 slide for a 1.5min pitch in the Room NAFSIKA during the pitching session preceding their poster presentation as indicated in the program. The slides should be sent to the email address of the conference fosbe2024@iceht.forth.gr by 10PM of Sunday September 8 for the presenters of poster session I and by 10PM of Monday September 9 for the presenters of poster session II. All presenters should also be present in front of their poster during the poster session to explain their work and to interact with fellow attendees.

Best Student Poster Awards: 2 student awards for the best posters *presented* by a student or post-doc will be given during the closing session, consisting of a certificate and a 100 Euros stipend. Frontiers in Systems Biology offers the possibility for the awardees to serve as topic coordinators in one of the two topics of the journal associated with FOSBE2024 with a certificate of recognition given to the young investigator upon completion by Frontiers.

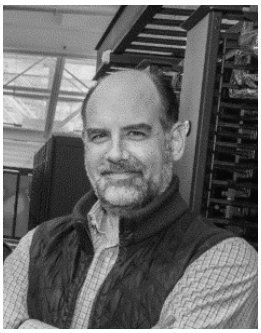
Session Chairs

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 13th minute of presentation for regular presentations) to start making 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.

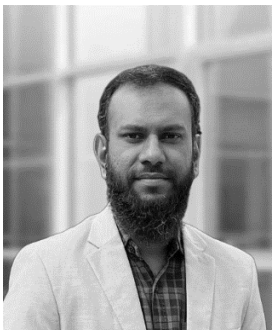
Keynote Speakers



Nikos Kyrpides
Lawrence Berkeley National Laboratory, US
https://jgi.doe.gov/our-science/scientists-jgi/nikos-kyrpides/

Microbiome Data Science: From the Earth Microbiome to the Global Virome

Abstract: The field of microbiome research is experiencing a transformative shift towards Data Science, propelled by the massive influx of microbiome data. This burgeoning volume of data presents both formidable challenges in terms of establishing standards and management frameworks, and simultaneously unlocks unprecedented opportunities for groundbreaking discoveries. Our current exploration into computational analysis of microbiome samples, including those from previously uncultured organisms, is significantly enriching our understanding of microbial community structures and functions. This, in turn, is broadening our grasp of the genetic and functional diversity within individual microorganisms. In this talk, I will elucidate our cutting-edge computational methodologies, underscoring the pivotal role of big data processing and integration in mining metagenomic datasets. Such approaches are instrumental in unveiling novel insights and fostering discoveries. I will detail our latest strategies for data analysis and share illustrative science vignettes that highlight the exploration of microbial, viral, and functional diversities. Through this talk, I aim to showcase the transformative potential of integrating big data with microbiome research, paving the way for scientific breakthroughs in understanding the complexity and dynamism of microbial ecosystems.



Rahuman Sheriff
European Bioinformatics Institute Cambridge, UK
https://fosbe2024.iceht.forth.gr/index.php/speaker/rahuman-sheriff/

Two Decades of BioModels: Promoting FAIReR Sharing and Reproducibility of Computational Models in the Life Sciences

Abstract: BioModels is a world-leading repository of computational models in the life sciences. Over the past two decades, BioModels has evolved from primarily curating ODE-based kinetic models to curating models across diverse modelling approaches. Originally established in 2005, BioModels now serves as a key repository for a wide range of computational models, ensuring they are Findable, Accessible, Interoperable, Reusable, and, more importantly, Reproducible (FAIReR). To investigate the reproducibility crisis in systems biology modelling, BioModels systematically attempted to reproduce 455 kinetic models published in peer-reviewed research articles. The study revealed that nearly half (49%) of these models could not be reproduced using the information provided in the manuscripts. This analysis exposed a widespread problem in the peer-review process, leading BioModels to propose an 8-point reproducibility scorecard to help authors, reviewers, and editors address this crisis. BioModels has developed several specific initiatives to address reproducibility challenges across different model types: (i) In constraint-based models, such as genome-scale metabolic models (GEMs), flux values reported in manuscripts are often not unique, making it difficult to numerically reproduce these models. To address this, BioModels developed the FROG analysis, which standardizes model evaluation and improves reproducibility by facilitating the public sharing of reference datasets. (ii) Stochastic models generate different numerical outcomes with each run, complicating the assessment of their reproducibility. The EFECT method was created to evaluate the reproducibility of stochastic simulation results by assessing whether the distributional differences in outcomes are consistent and reproducible. (iii) Machine learning (ML) models, along with their datasets and associated tools, are often scattered across various platforms and sometimes incomplete, complicating the process of assembling them and reproducing results. The BioModels-ML project was launched to standardize and streamline the sharing of ML models, ensuring they are FAIR and reproducible.

Invited Speakers

Ioannis (Yannis) P. Androulakis
Rutgers University, US
https://bme.rutgers.edu/ioannis-yannis-p-androulakis

It's All about Time! the Critical Role of Circadian Rhythms in Regulating Health, Disease, and Pharmacology

Marc Biarnes Carrera
ProKarium, UK
https://www.prokarium.com/

Living Cures: Building a Programmable Therapeutic Platform for Optimization and Delivery of Immunostimulatory Proteins

Livija Deban
Prokarium, UK
https://www.prokarium.com/

Living Cures: Building a Programmable Therapeutic Platform for Optimization and Delivery of Immunostimulatory Proteins

Davide Fiore
University of Naples Federico II, IT
https://www.matematica.unina.it/

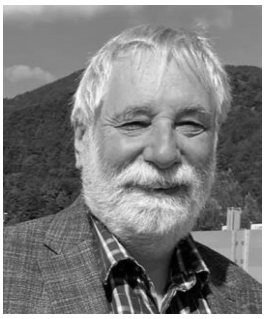
Feedback Control of Microbial Consortia

Rennos Fragkoudis
University of Edinburg, UK
https://www.ed.ac.uk/biology/research/facilities/edinburgh-genome-foundry

Robots & DNA: The Edinburgh Genome Foundry

Traci Haddock
Asimov Inc., US
https://www.asimov.com/

ASIMOV: Intelligent Design of Living Systems



John Hancock,
University of Ljubljana, SI
http://cfgbc.mf.uni-lj.si/

Massimo Lai,
AstraZaneca, UK
https://www.astrazeneca.co.uk/

T-Cell Engagers: Some Lessons Learned from a Minimal Mechanistic Model of Trimer Formation

Tereza Manousaki
HCMR, GR
https://imbbc.hcmr.gr/user/tereza/

Taming the Genomic Era and Democratising Bioinformatics to Face Biodiversity Challenge

Barbara Szomolay,
University of Cardiff, UK
https://profiles.cardiff.ac.uk/staff/szomolayb

Computational Identification of Cancer Immunotherapy Targets

Shihui Yang,
Hubei University, CN
https://fosbe2024.iceht.forth.gr/index.php/speaker/shihui-yang/

ZymOmics: A One-Stop Omics Database of Zymomonas Mobilis

FOSBE2024 Awards

FOSBE AWARD 2024

Jesus Pico
Technical University of Valencia, US
https://gcsc.ai2.upv.es//content/jesus.html

Synthetic Biology and Biosystems Control

Frontiers in Systems Biology Young Investigator Award associated with FOSBE 2024

Ashti Shah
University of Pittsburgh, US

https://fosbe2024.iceht.forth.gr/index.php/speaker/ashti-shah/l

Computational Inference of Chemokine-Mediated Roles for the Vagus Nerve in Modulating Intra- and Inter-Tissue Inflammation

Program and Abstracts Sunday September 8, 2024

14:30-15:00 SuAT1 Room NAFSIKA **Opening Remarks** *Maria I. Klapa*, FORTH/ICE-HT, Greece
15:00-16:00 SuBT1 Room NAFSIKA **Keynote Lecture I** **Microbiome data science: from earth microbiome to global virome** *Nikos Kyrpides*, DOE Joint Genome Institute, Lawrence Berkeley National Laboratory, USA
16:00-17:10 SuCT1 Room NAFSIKA **General Session 1** – **Modeling Microbial Systems** *Session Chair: Kristel Bernaerts, KU Leuven, Belgium*
17:10-17:40 Coffee Break
17:40-18:30 SuDT1 Room NAFSIKA **General Session 1** – **Modeling Microbial Systems** *Session Chair: Kristel Bernaerts, KU Leuven, Belgium*
18:30-19:00 SuET1 Room NAFSIKA **Invited Lecture 3** – **Taming the Genomic Era and Democratising Bioinformatics to Face Biodiversity Challenges** *Tereza Manousaki, HCMR, Greece*
19:00-20:00 SuFT1 Room NAFSIKA **FOSBE AWARD PRESENTATION** ***Chairs:*** *Maria I. Klapa, FORTH/ICE-HT, Greece;* *Alejandro Vignoni, Universitat Politécnica de València, Spain* ***Synthetic Biology and Biosystems Control*** Jesus Pico, Universitat Politécnica de València, Spain
20:30-23:00 SuGT1 Veranda PERGOLA **Welcome Reception**

Technical Program for Sunday September 8, 2024

SuAT1 Room NAFSIKA

Opening Session

14:30-15:00

Opening Remarks

Klapa, Maria I.

NOC Chair, Institute of Chemical Engineering Sciences, Foundation for Researc & Technology, Hellas (FORTH/ICE-HT), Greece

SuBT1 Room NAFSIKA

Keynote Lecture I (Keynote Session)

Chair: Klapa, Maria — Foundation for Research and Technology-Hellas

15:00-16:00 SuBT1.1

Microbiome Data Science: From the Earth Microbiome to the Global Virome, pp. 1-1

Kyrpides, Nikos

The field of microbiome research is experiencing a transformative shift towards Data Science, propelled by the massive influx of microbiome data. This burgeoning volume of data presents both formidable challenges in terms of establishing standards and management frameworks, and simultaneously unlocks unprecedented opportunities for groundbreaking discoveries. Our current exploration into computational analysis of microbiome samples, including those from previously uncultured organisms, is significantly enriching our understanding of microbial community structures and functions. This, in turn, is broadening our grasp of the genetic and functional diversity within individual microorganisms. In this talk, I will elucidate our cutting-edge computational methodologies, underscoring the pivotal role of big data processing and integration in mining metagenomic datasets. Such approaches are instrumental in unveiling novel insights and fostering discoveries. I will detail our latest strategies for data analysis and share illustrative science vignettes that highlight the exploration of microbial, viral, and functional diversities. Through this talk, I aim to showcase the transformative potential of integrating big data with microbiome research, paving the way for scientific breakthroughs in understanding the complexity and dynamism of microbial ecosystems.

SuCT1 Room NAFSIKA

Session 1: Modelling Microbial Systems (Regular Session)

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

16:00-16:30 SuCT1.1 (Invited Lecture 1)

Feedback Control of Microbial Consortia, pp. 2-2

Fiore, Davide; Salzano, Davide; di Bernardo, Mario

Synthetic biology aims at engineering biological systems with new functionalities, with applications ranging from personalized health treatments to bioremediation and the production of biofuels and drugs in bioreactors. This is made possible by designing artificial genetic circuits and embedding them into living cells, such as bacteria or yeast, changing their natural behavior, that is by modifying when and how much genes are expressed to produce proteins or other chemicals of interest. However, the level of complexity and the functions of such engineered genetic circuits are limited by intrinsic factors in the host cells, such as excessive metabolic burden, competition of limited resources and incompatible chemical reactions. To overcome these limitations, a promising strategy is to distribute the required functionalities among multiple cell populations, forming a microbial consortium, so that each cell strain embeds a smaller subset of engineered gene networks. However, this comes at the cost of engineering more complex systems in which each actor involved, i.e., a microbial species, cooperates with the others, sharing resources for their growth and communicates to maintain the community in health and the rate of bioreactions at the desired level. Therefore, the new challenge is to develop new feedback control strategies inside the microbial community to guarantee, at the same time, cooperation, communication, stable coexistence between the species involved, and reliable and robust bioproduction.

16:30-16:50 SuCT1.2 (OP1)

Spatiotemporal Modeling of a Synthetic Microbial Community During Colony Expansion, pp. 3-3

Sahin, Asli; Pignon, Estelle; Schaerli, Yolanda; Hatzimanikatis, Vassily

In nature, microorganisms are often found in communities composed of multiple species interacting with each other and their environment in complex networks. Microorganisms take up nutrients from their environment to grow and divide, forming spatially structured communities such as cellular aggregates or biofilms. The structure of these communities is dynamic, evolving due to local interactions between the community members and local variations in concentrations of nutrients and microbial species. As a result, microbial communities exhibit a non-random spatial arrangement, a phenomenon often termed as spatial self-organization. These spatial patterns exhibited by microbial communities are important indicators of community-level functions. They can determine the productivity of the community, metabolic interactions that are taking place, ecological and evolutionary processes, and the resistance to perturbations. Therefore, understanding the factors that influence the spatial arrangement of microbial communities is crucial for gaining deeper insights into the overall functioning and behavior of microbiomes. However, our current knowledge of factors that influence the formation of spatial patterns in microbial communities is still limited.

In this study, we expanded the previously developed agent-based modeling framework CROMICS (Angeles-Martinez, Hatzimanikatis, 2021) to study two-dimensional range expansion of a synthetic microbial community composed of two auxotrophic Escherichia coli strains. To this end, we combined Monod-type growth kinetics with the CROMICS framework and investigated the effects of perturbations on nutrient availability, initial conditions and biochemical parameters such as the uptake and leakage rates during colony expansion. We calibrated our model to align with experimental findings observed through microscopy images. We assessed the resulting patterns by quantifying the emergent properties of the colonies, such as interaction range, intermixing, colony radius and species abundances. Overall, our results elucidate the relative effects of uptake and leakage rates on spatial patterns and provide deeper insights into the underlying factors governing the spatial organization and behavior of microbial communities.

16:50-17:10 SuCT1.3 (OP2)

A Pipeline for Calibrating Agent-Based Models of Microbial Populations: From Image Collection to Model Parameterization, pp. 4-9

Ahmadi, Atiyeh; Yip, Aaron; Chalaturnyk, Jonathan; Aucoin, Marc; Ingalls, Brian P.

We present a framework for calibration of agent-based models of bacilliform (rod-shaped) bacterial populations based on time-lapse microscopy at single-cell resolution. Our approach draws on pattern-oriented modelling for feature selection, followed by sensitivity analysis and Bayesian inference to arrive at a model calibration that aligns with experimental observations. We illustrate this pipeline by calibrating a model of microcolony formation against observations of monolayer E. coli population growth.

17:10-17:40 Room NAFSIKA

Coffee Break

SuDT1 Room NAFSIKA

Session 1 (cont'd): Modelling Microbial Systems (Regular Session)

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

17:40-18:00 SuDT1.1 (OP3)

Comprehensive Theory of (microbial) Community Growth in Constraint-Based Modeling, pp. 10-10

Müller, Stefan; Mießkes, Marianne; Zanghellini, Juergen; Széliová, Diana

Microbial communities are increasingly recognized for their significance in human health, ecology, and biotechnological applications. However, their inherent complexity presents challenges for laboratory studies. Metabolic modeling offers a promising avenue for overcoming these challenges by providing a holistic, system-level understanding of microbial community dynamics, including community compositions, growth rates, and feeding interactions among individual members.

While constraint-based (COBRA) methods such as flux balance analysis (FBA) and elementary flux modes/vectors (EGMs/EGVs) have been widely used to characterize the metabolic capabilities of single organisms, their application to microbial communities has been hindered by the lack of rigorous mathematical definitions for the community context.

Here, we close this gap and introduce a formal definition of a constraint-based community model that enables direct application of existing COBRA methods. Moreover, by projecting the community model onto microbial mass fractions and exchange fluxes, we derive growth-rate-dependent elementary composition vectors and elementary exchange flux vectors that seamlessly extend the elementary pathway concepts to communities. More specifically, these vectors facilitate the minimal reconstruction of all feasible community compositions and their associated exchange fluxes. We demonstrate how these elementary vectors capture essential community interactions such as specialization, mutualism, and commensalism. Notably, distinct behaviors emerge based on growth rate and community composition.

In summary, we present a mathematically sound and consistent theory of constraint-based analysis of (microbial) communities and extend the concepts of elementary modes and vectors to microbial communities, offering fundamental insights into their dynamic behaviors, and allowing rational design of microbial communities.

18:00-18:30 SuDT1.2 (Invited Lecture 2)

ZymOmics: A One-Stop Omics Database of Zymomonas Mobilis, pp. 11-11

Yang, Shihui

Zymomonas mobilis, a Gram-negative ethanologenic bacterium with unique features, has been developing as cell factories for cellulosic ethanol and diverse biochemicals. Since its genome was sequenced in 2005, a significant amount of omics data has been accumulating, which is calling for the development of an all-inclusive database for organizing, retrieving, mining, and analyzing these datasets. An integrated omics database of Z. mobilis, ZymOmics (http://zymomics.cn), was developed in this study, which contains comprehensive information for 2001 gene entries of Z. mobilis subsp. mobilis ZM4 including genome location, gene information, and gene/protein expression values from different omics studies. In addition, ZymOmics also includes potential homologues for each gene of ZM4 in E. coli and S. cerevisiae, protein-protein interactions predicted by the STRING database, and structures of all proteins predicted by AlphaFold2. ZymOmics

also contains 191 biological parts of Z. mobilis collected from literature and iGEM Parts Registry. Moreover, ZymOmics provides three NGS data analysis workflows, website information on commonly used bioinformatics tools, and literature resources that is updated automatically. Our study thus not only developed ZymOmics, a web-hub of omics datasets and related information of Z. mobilis, but also provides a paradigm to develop a species-specific one-stop database for other non-model microorganisms.

SuET1	Room NAFSIKA
Invited Lecture 3 (Regular Session)	
Chair: Bernaerts, Kristel	University of Leuven (KU Leuven)
18:30-19:00	SuET1.1

Taming the Genomic Era and Democratising Bioinformatics to Face Biodiversity Challenges, pp. 12-12

Manousaki, Tereza

Our planet is experiencing the sixth mass extinction, a joint result of habitat degradation, climate crisis and human-assisted species invasions. The challenges we face are complex and demand action on multiple fronts to mitigate the impact of biodiversity loss. In this battle, the major breakthroughs in sequencing, bioinformatics and OMICs technologies have been proven invaluable tools that can be employed to inform the societal response to those challenges. Genomics has transformed biology, moving beyond model species and offering unprecedented opportunities in understanding the ecological and evolutionary processes. Whole genome sequencing efforts, such as the European Reference Genome Atlas (ERGA), are being launched globally and contribute to the transition to an era where data availability will not be a limiting factor any more. This talk will include an overview of the community efforts to deal with the biodiversity related data explosion, both at the European level through ELIXIR Europe, the European infrastructure for life science data, as well as at the national level through MBGC, the network on Molecular Biodiversity Greece Community. First, within the framework of ELIXIR Europe, and in particular in the context of the Science Priority Area on Biodiversity, Food Security and Pathogens, we are building a strategy that will benefit the research community in data management, data analysis and training. At the national level, MBGC has formed a network of networks bringing together researchers in the field of molecular biodiversity, aiming to identify the needs of the local researchers, accelerate the search for sustainable solutions and strengthen the interaction among them. These efforts, combined with other approaches globally can greatly facilitate our understanding and better management of biodiversity.

SuFT1	Room NAFSIKA
FOSBE Award Presentation	
Chair: Klapa, Maria	Foundation for Research and Technology-Hellas
Co-Chair: Vignoni, Alejandro	Universitat Politècnica De Valencia
19:00-20:00	SuFT1.1

Synthetic Biology and Biosystems Control

Picó, Jesús

Presented by Jesús Picó, head of the Synthetic Biology and Biosystems Control Lab (SB2CL) at UPV and recipient of the FOSBE Award 2024, this talk will explore cutting-edge research at the intersection of systems engineering, synthetic biology, and industrial bioprocesses. The focus will be on innovative approaches to optimizing the Design-Build-Test-Learn (DBTL) cycle, dynamic gene expression regulation, metabolic network analysis, and bioprocess control. Attendees will gain insights into how these advancements are revolutionizing biofabrication and the development of complex chemical pathways.

20:30-23:00	**Veranda PERGOLA**
Welcome Reception	

Program and Abstracts Monday September 9, 2024

09:00-10:50 MoAT1
Room NAFSIKA
General Session 2 – **Synthetic Biology**
Session Chair: Alejandro Vignoni

10:50-11:10 Coffee Break

11:10-12:10 MoBT1
Room NAFSIKA
Panel Discussion 1 – **Systems & Synthetic Biology: Innovation & Entrepreneurship**
(Moderator: Livija Deban, Prokarium, UK)
Panelists:
Alejandro Vignoni, Technical University of Valencia, Spain
Nikos Kyrpides, DOE JGI, Lawrence Berkeley National Lab, USA
Marc Biarnes Carrera, Prokarium, UK
Traci Haddock, Asimov Inc., USA
Massimo Lai, Astrazeneca, USA
Spyros Vernardis, Eliptica Limited, UK

12:30-17:30
Excursion in the Island by bus including Lunch

18:00-18:45 MoCT1
Room NAFSIKA
FRONTIERS IN SYSTEMS BIOLOGY YOUNG INVESTIGATOR AWARD
ASSOCIATED WITH FOSBE 2024
Chair: Maria I. Klapa, FORTH/ICE-HT, Greece
Frontiers in Systems Biology: Breaking Down Silos and Integrating Datasets, Toolsets, and Mindsets in Partnership with FOSBE | Inauguration of the Young Investigator Award
Yoram Vodovotz, Field Chief Editor & *Thomas C. Collin*, Journal Manager
AWARD PRESENTATION:Computational Inference of Chemokine-Mediated Roles for the Vagus Nerve in Modulating Intra- and Inter-Tissue Inflammation
Ashti Shah, School of Medicine, University of Pittsburgh, USA

18:45-19:30 MoDT1
Room NAFSIKA
POSTER SESSION I - Pitches
Chair: Spyridon (Spyros) Aleiferis, Complexity Cybernetics SPPC, Greece

19:30-21:00 MoET1
Room CALYPSO
POSTER SESSION I - Presentations + Wine & Cheese Buffet

Technical Program for Monday September 9, 2024

MoAT1 Room NAFSIKA
Session 2: Synthetic Biology (Regular Session)
Chair: Vignoni, Alejandro — Universitat Politècnica De Valencia

09:00-09:30 MoAT1.1 (Invited Lecture 4)

*Robots & DNA: The Edinburgh Genome Foundry**
Rennos, Fragkoudis

Biofoundries encourage the use of cutting-edge computational tools and automated workflows that are key to accelerating the engineering of biological systems. The Edinburgh Genome Foundry (EGF) at the University of Edinburgh is a core research facility that provides academic and industrial customers access to state-of-the-art equipment and automation infrastructure. We specialise in the miniaturised assembly of DNA constructs for fundamental and biotechnology-related research using a fully automated workflow on our highly integrated robotics platform. A custom suite of computational tools is utilised to automate the design of DNA sequences and facilitates interactions between the robotic platform, databases, and user interfaces in processes from project onboarding to quality control procedures. In addition to DNA assembly, the platform and integrated liquid handling systems are used for high-throughput automation of common molecular biology protocols, micro-organism handling, and the development of bespoke assays. These workflows are complemented either by in-house instrumentation or through collaborations with internal research facilities for additional phenotypic screening such as next-generation sequencing, proteomics, and metabolomics.

EGF's Beacon Optofluidics system from Bruker Cellular Analysis is an outstanding addition to our portfolio. The Beacon platform allows the simultaneous analysis of thousands of cells in isolated chambers and enables users to implement workflows used for antibody discovery and cell line development. As the only instrument of its kind in a European academic facility, EGF's investment in the Beacon system has provided our stakeholders with unparalleled access to state-of-the-art technology to perform high-throughput single-cell screening experiments.

Our advanced computational tools and automation technologies have been crucial in research projects such as gene therapy, vaccine development, and metabolic engineering. Expanding our toolkit to include the Beacon system is key to facilitating the development of previously unfeasible projects in both academia and industry.

09:30-09:50 MoAT1.2 (OP4)

Designing High Performance Whole Cell Biosensors by Integrating Synthetic Biology with Control Engineering, pp. 13-13

Fusco, Virginia; Fiore, Davide; di Bernardo, Mario; di Bernardo, Diego

Transcription-based whole-cell biosensors (WCBs) are cells engineered with an analyte-responsive promoter driving the transcription of a reporter gene. WCBs can sense and report on bioactive molecules (analytes) relevant to human health. Designing an analyte-sensitive promoter requires a cumbersome trial-and-error approach and usually results in biosensors with poor performance. Here we first abstracted biosensors as input (analyte)-output(reporter protein) dynamical systems. We then defined five quantitative metrological features to gauge their performance from the input-output response: Leakiness, Fold-Change, Operation Range, Sensitivity and Linearity. To design biosensors with improved performances, we developed a theory-driven approach that integrates Synthetic Biology and Control theory techniques to design and test WCBs with improved metrological features. Analytical solutions and quantitative modelling were used to investigate the properties of eight distinct biomolecular circuits incorporating different combinations of known and novel gene network motifs, such as Feed Forward Loops (FFLs), Negative Feedback Loops (NFLs) and Mutual Inhibition (MI) endowing the system with the desired properties. Through both analytical and numerical analyses, we established that the NFL motif acts orthogonally to the MI and FFL motifs in terms of improving biosensor features. Specifically, the NFL motif confers increased linearity and operation range, whereas leakiness, sensitivity and fold-change are improved by the MI and FFL motifs. We also found that one of the eight gene networks, combining the NFL, MI and FFL motifs closely approximates an ideal biosensor exhibiting minimal leakiness with no reduction in the maximum reporter expression, a linear dose-response curve, high sensitivity and high fold-change.

The significance of our work lies in its potential to impact the monitoring of bioactive molecules and chemicals both in vitro and in vivo, which is crucial in areas such as toxicology, drug discovery, disease diagnosis and therapy.

09:50-10:10 MoAT1.3 (OP5)

DBTL Bioengineering Cycle for Part Characterization and Refactoring, pp. 14-19

Arboleda-Garcia, Mario Andres; Stiebritz, Martin; Boada, Yadira; Picó, Jesús; Vignoni, Alejandro

The Design-Build-Test-Learn (DBTL) cycle is a crucial framework in Synthetic Biology for the development and optimization of biological systems. However, the manual nature of the cycle poses limitations in terms of time and labor. This paper focuses on the application of automation techniques to the DBTL cycle, specifically in the testing and characterization of standard bioparts, which are essential components of genetic circuits. By automating the testing process, throughput, reliability, and reproducibility can be significantly improved. This paper discusses the challenges associated with manual testing methods and explores various automation strategies and technologies that can address these challenges. High-throughput screening methods, laboratory robotics, and data analysis algorithms are key elements in the automation process. As a case study, we utilize the automated DBTL cycle to refactor a biosensor, aiming to enhance its performance. Integrating automation in the DBTL cycle offers numerous advantages, including increased efficiency, standardization, and quality control of bioparts. It also enables the exploration of larger design spaces and rapid prototyping of complex genetic systems. Here, we show the advantages of using the DBTL cycle to refactor a biosensor that presents improved performance and can be readily used in more complex circuits.

10:10-10:30 MoAT1.4 (OP6)

Controlling Gene-Expression Variability Via Sequestration-Based Feedbacks, pp. 20-25

Dey, Supravat; Vargas-Garcia, Cesar Augusto; Singh, Abhyudai

Expressed Transcription Factors (TFs) not only bind to sites at target promoters but also to decoy sites scattered across the genome. Binding to such ``decoys'' sequesters TFs critically impacting the response time and stochasticity (noise) in TF and target gene expression level. When the TF is a stable molecule, whose concentration is diluted by cellular growth, our results show that for fixed mean concentration levels, such decoy bindings can both enhance or suppress random fluctuations in TF levels depending on the source of noise (i.e., intrinsic vs. extrinsic noise) and the strength of binding (i.e., weak vs. strong decoys). We implement negative autoregulation where free (unbound) TF molecules inhibit their synthesis. Our analytical results corroborated by numerical simulations reveal that sequestration accentuates the effects of feedback in the sense that noise attenuation by negative feedback is higher with sequestration than in the absence of feedback. We next consider an alternative form of feedback where the TF increases the production of its decoys, and such feedback architectures are frequently seen in endogenous gene regulation involving microRNA-TF circuits and in controlling cellular stress responses. For these circuits where decoy numbers are TF-regulated, we identify limits of noise suppression, and in many cases, these limits occur at intermediate TF-decoy binding affinities.

10:30-10:50 MoAT1.5 (OP7)

Marginal Percentile Intervals in Bayesian Inference Are Overconfident, pp. 26-31

Höpfl, Sebastian; Tautenhahn, Hans Michael; Wagner, Vincent; Radde, Nicole

In Bayesian statistics, Highest Posterior Density Regions (HPDR) measure the uncertainty of parameter estimates at a given credibility level. HPDRs are the Bayesian version of Highest Density Intervals (HDI) based on the posterior probability. The calculation of Percentile Intervals (PI) is a common method for approximating HDIs in many popular Python toolboxes. The PI calculation differs from the HPDR calculation as it ignores the posterior probability by simply cutting the lower and upper values of the marginalized posterior distribution symmetrically. Here, we use the phenomenological retarded transient functions to infer the posterior distribution of a clinical dataset. The one-dimensional HPDR projections were compared to the PIs for all inferred parameters. The direct comparison revealed that the one-dimensional HPDR projections of all inferred parameter posteriors exceeded the percentile-based intervals, demonstrating that the PIs were overconfident. Overall, we argue that only HPDRs can be interpreted in terms of probability.

10:50-11:10 Room NAFSIKA

Coffee Break

MoBT1 Room NAFSIKA

Panel Discussion I: Systems & Synthetic Biology - Innovation & Entrepreneurship

Moderator: Deban, Livija Prokarium

11:10-12:10

Panelists

Vignoni, Alejandro, Technical University of Valencia, Spain
Kyrpides, Nikos, DOE JGI, Lawrence Berkeley Nat. Lab, USA
Biarnes Carrera, Marc, Prokarium, UK
Haddock, Traci, Asimov Inc., USA
Lai, Massimo, Astrazeneca, USA
Vernardis, Spyros, Eliptica Limited, UK

12:30-17:30

Excursion in the Islalnd by bus including Lunch

MoCT1 Room NAFSIKA

FRONTIERS IN SYSTEMS BIOLOGY YOUNG INVESTIGATOR AWARD ASSOCIATED WITH FOSBE 2024

Chair: Klapa, Maria — Foundation for Research and Technology-Hellas

18:00-18:20 MoCT1.1

*Frontiers in Systems Biology: Breaking Down Silos and Integrating Datasets, Toolsets, and Mindsets in Partnership with FOSBE | Inauguration of the Young Investigator Award**

Vodovotz ,Yoram; Collin, Thomas C

18:20-18:45 MoCT1.2

*Award Presentation: Computational Inference of Chemokine-Mediated Roles for the Vagus Nerve in Modulating Intra- and Inter-Tissue Inflammation**

Shah, Ashti

Computational immunology offers a set of tools to facilitate the modeling of cross-tissue inflammation across time. Traditional statistics have been leveraged in algorithms such as dynamic Bayesian networks, dynamic network analysis, and dynamic hypergraphs. These models can provide unique insights when considering the human body as a 4-dimensional space, namely the three physical dimensions of the body as well as time. Advanced machine learning approaches utilizing so-called “artificial intelligence” (AI) have been used for systems immunology in the context of single-cell ‘omics, but have not proven useful for more common, smaller datasets. We have drawn inspiration from AI models used to analyze 3D videos to structure our datasets composed of concentrations of inflammatory mediators in multiple organs across several time points. The application of traditional statistics to this unique data-setup, viewing the human body in 4D, has resulted in numerous novel insights regarding the spatiotemporal spread of inflammation in pathologies such as sepsis, trauma, as well as for assessing the role of the vagus nerve in regulating cross-tissue inflammation. One study in specific sought to model the effects of vagotomy on cross tissue inflammation. The vagus nerve innervates multiple organs, but its role in regulating cross-tissue spread of inflammation is unclear. We hypothesized that the vagus nerve may regulate cross-tissue inflammation via modulation of the putatively neurally regulated chemokine IP-10/CXCL10. Rate-of-change analysis, dynamic network analysis, and dynamic hypergraphs were used to model intra- and inter-tissue trends, respectively, in inflammatory mediators from mice that underwent either vagotomy or sham surgery. This analysis suggested that vagotomy primarily disrupts the cross-tissue attenuation of inflammatory networks involving IP-10 as well as the chemokines MIG/CXCL9 and CCL2/MCP-1 along with the cytokines IFN-□ and IL-6. Computational analysis also suggested that the vagus-dependent rate of expression of IP-10 and MIG/CXCL9 in the spleen impacts the trajectory of chemokine expression in other tissues. Perturbation of this complex system with bacterial lipopolysaccharide (LPS) revealed a vagally regulated role for MIG in the heart. Further, LPS-stimulated expression of IP-10 was inferred to be vagus-independent across all tissues examined while reducing connectivity to IL-6 and MCP-1, a hypothesis supported by Boolean network modeling. Together, these studies define novel spatiotemporal dimensions of vagus-regulated acute inflammation.

18:45-19:30 **MoDT1**

Poster Session I - Pitches Room NAFSIKA

Chair: Aleiferis, Spyridon — Complexity Cybernetics SPPC

MoDT1.1 (P1.1)

in Silico Functional Comparison of the Leaf Microbiome by Reducing Metabolic Complexity, pp. 32-32

Vayena, Evangelia; Pacheco, Alan; Vorholt, Julia A.; Hatzimanikatis, Vassily

The assembly and function of microbiomes depend on differences in the metabolic capabilities of member strains, which can lead to the emergence of positive or negative interspecies interactions. As microbiome structure is linked to host health and ecosystem function, understanding how these differences underly observed phenotypes can inform targeted microbiome engineering strategies for health and environmental applications. The inherent complexity of cellular metabolism necessitates the use of mathematical models and computational methods in the study of microbiomes.

In this study, we use a collection of curated genome-scale metabolic models (GEMs) of the Arabidopsis thaliana leaf microbiome (1) and a computational workflow to systematically compare the metabolic requirements and capabilities of the different strains. Our approach leverages GEM reduction algorithms (2-4) to reduce the complexity of metabolic networks to simpler modules and facilitate the comparative analysis of metabolism. We use the results of this comparison to identify strains that exhibit similar metabolic profiles, suggesting the formation of functional guilds. We further leverage the data to identify the metabolic traits of each strain associated with experimentally observed interaction outcomes in planta.

Our approach can be applied to any microbiome to identify functional guilds and strains with complementary metabolic traits, contributing to the design of synthetic communities with enhanced biosynthetic or biodegradative performance, as well as communities that protect from pathogens.

MoDT1.2 (P1.2)

Shining Light on Single-Cell Dynamics and Heterogeneity: Design and Analysis of a Hybrid Population Model for an Epigenetic Memory System, pp. 33-33

Klingel, Viviane; Radde, Nicole

Heterogeneity in biological systems can be quantified efficiently by single-cells measurement techniques like flow cytometry. However, many modelling approaches currently cannot capture this behavior, as often only the average cell is covered in commonly used ODE models. Single-cell data can be reduced to summary statistics for use with these models, but this leads to a loss of information in the data and, more importantly, only provides a complete description if the data is close to a normal distribution. Especially in the case of bimodal distributions, which can for example occur in bistable systems, averages are poor descriptions of the data and lack the ability to reproduce important features of the system.

The synthetic epigenetic memory system from Graf et al. (2022) is such a particular system. It is characterized by the ability to switch from an OFF- to an ON-state through a transient metabolic trigger. This ON-state is sustained via positive feedback based on DNA methylation. A large part of the cells can remember this state for many days, but eventually, more and more cells switch back to the OFF-state. In the experimental data, this is observable as a transient appearance of two subpopulations, ON- and OFF-cells, with a drift towards the OFF state. We aim to capture this transient bimodality by a tailored model which describes heterogeneous single-cell trajectories. Our hybrid model combines the simulation speed of differential equations with a stochastic process describing cell division, as well as distributed parameters and measurement noise. We trained the model by comparing the simulated population to the data using the Kolmogorov metric, a shape sensitive distance between distributions. The model reproduces the experimental single-cell data as well as bulk methylation measurements well and is able to predict previously unseen data, including experiments of cyclic ON-OFF-switching with an additional input. Our trained model provides insights into the switching behavior and in particular the mechanisms behind the drift towards the OFF-state on the population and on the single-cell scale. Our analysis suggests that the stochastic nature of the cell division plays an important role in the destabilization of the ON-state, but its effect is only observable over long time.

MoDT1.3 (P1.3)

From Receptors to Metabolism: Reconstruction and Analysis of Information Flow in Large-Scale Signaling Networks, pp. 34-34

Liaskos, David; Masid Barcon, Maria; Oftadeh, Omid; Hatzimanikatis, Vassily

Cells receive and respond to various signals through a complex network of signaling pathways, ultimately regulating gene expression and cellular physiology. The advent of high throughput

technologies enabled the description of numerous signaling mechanisms. However, understanding the properties that influence the information flows at the cellular level requires integrating several pathways and mathematically describing the interactions between the components of these pathways. To enable the study of signaling events that influence cell metabolism, we developed a method for reconstructing large-scale signaling networks and a mathematical formulation for guiding the signal through this network. Starting from the biological information in the Reactome database, we reconstruct signaling networks by selecting the species of interest and collecting the relevant pathways. After carefully reconstructing the signaling network, we navigate the signal from a receptor to the target proteins using a linear programming method. Our method identifies the components necessary for direct signal transduction and addresses the necessity of understanding the contribution of the peripheral pathways to sustain the operation of such signaling cascades. This approach paves the way towards understanding quantitatively the importance of cross-talking using elementally balanced signaling networks. We applied our method to study how activation of neurotrophic tyrosine kinase receptors (NTRKs) affects, in alternative ways, key metabolic proteins such as mTOR and AMPK that regulate the activity of several transcription factors. Finally, our method offers the future basis for integrating multi-omics data to study the interconnection between cellular signaling and metabolic regulation and for creating models to predict the dynamic properties of signal transduction.

MoDT1.4 (P1.4)

Model-Based Optimization of Yeast Batch Fermentation: Toward a Digital Twin for the Winemaking Industry, pp. 35-36

Rodríguez Moimenta, Artai; Minebois, Romain; Ramirez Aroca, Lainy; Querol, Amparo; Balsa-Canto, Eva

The biotechnology industry can benefit greatly from implementing digital twins (DT) in fermentation processes. The core of DT is an accurate mathematical model. However, the complexity of modelling batch fermentation, particularly in food-related applications, in which secondary metabolism is relevant, still need to be addressed. Here, we present the first steps toward developing a digital twin for the winemaking sector. Our approach combines a kinetic model that accounts for secondary metabolism and the role of temperature with multi-objective optimisation to select the best industrial starter and operation conditions for a given grape must. We illustrate the performance of the approach for an industrially relevant yeast species. Our results show that the winemaking industry can achieve greater efficiency, higher-quality products, and reduce environmental impact by embracing digital twins.

MoDT1.5 (P1.5)

Engineering Zymomonas Mobilis for Bioplastic Precursors Production, pp. 37-37

He, Qiaoning

Global environmental concerns over waste plastics' effect on the environment are leading to the production of biodegradable plastics with industrial microorganisms. Zymomonas mobilis is a natural ethanologen known to use the Entner-Doudoroff (ED) pathway anaerobically with many unique physiology characteristics, which makes it an ideal industrial microbial cell factory. Here, we will introduce our efforts on developing Z. mobilis for bioplastic precursors such as bioproducts of D-lactate, 3-hydroxybutyrate and poly-3-hydroxybutyrate. The classical metabolic engineering strategies of using strong promoter and/or increasing the copy numbers, balancing cofactor supply, and introducing heterologous pathway for pathway precursors generation in Z.mobilis will be introduced. Process engineering approaches with C/N optimization, self-flocculating characteristics empowering and continuous co-production will also be discussed. In addition, we develop a high-throughput approach that combines genome-scale CRISPR interference (CRISPRi) and LldR-based D-lactate biosensor-assisted screening to identify genetic targets associated with D-lactate production in Z. mobilis. Efforts to optimize bioplastic precursors production with morphology engineering and molecular engineering will also be discussed. This study shows that by merging the synthetic biology and metabolic engineering strategies enable the production of bioplastic precursors efficiently and provide guidance for cell factories engineering in other industrial microorganisms.

MoDT1.6 (P1.6)

Identification of New Antimicrobial Resistance Genes in E. Coli through Network Diffusion, pp. 38-38

Mansouri, Anis; Durazzi, Francesco; Ahmed Ishan, Muhammad; Pasquali, Frederique; Valdramidis, Vasilis; Remondini, Daniel

Antimicrobial Resistance (AMR) is an emerging issue, related to the massive use of antibiotics in the last century for health and food safety, causing significant economic costs and probably becoming one of the first causes of death in the next decades. It is thus mandatory to better understand the AMR mechanisms within pathogens, possibly to develop novel drug and multidrug strategies involving novel targets. In our work, we used a systems biology approach consisting of network diffusion analysis to discover new AMR-related genes in E. coli. Starting from 34 AMR-related genes known from literature (CARD and PointFinder databases), we could identify a new list of 93 genes potentially associated with AMR then we selected thirteen genes for in vitro validation (susceptibility testing) in the presence of five different antibiotics. Four mutants showed a significant shift in their anti-microbial susceptibility. This work will contribute to a better understanding and characterization of AMR in E. coli to better control the spread of this phenomenon.

MoDT1.7 (P1.7)

Comparative System Identification of the Refuge Tracking Behavior in Weakly Electric Fish, pp. 39-40

Goksuluk, Eren Cem; Yilmaz, Onurcan; Uyanik, Ismail

This study investigates the application of system identification methods to understand the refuge tracking behavior of weakly electric fish. Five data-driven methods were compared: Frequency Response Function (FRF), Recursive Least Squares (RLS), AutoRegressive with eXogenous input (ARX), AutoRegressive Moving Average with eXogenous input (ARMAX), and N4SID (subspace identification). Results showed that N4SID, a subspace identification method, exhibited the best performance as compared to other methods in modeling complex refuge tracking dynamics.

MoDT1.8 (P1.8)

Nonlinear Dynamic Models Assisted Design of Recombinant Strains, pp. 41-41

Narayanan, Bharath; Weilandt, Daniel; Masid Barcon, Maria; Miskovic, Ljubisa; Hatzimanikatis, Vassily

Devising genetic interventions to achieve specific cellular phenotypes is challenging regarding time and resources. Although nonlinear dynamic models are well suited for this task because they can capture the metabolic responses of cells to genetic and environmental perturbations, they are rarely used due to difficulties in building and curating these models. Moreover, exhaustive simulation of cellular responses to putative strain designs with such large systems of ordinary differential equations, particularly when targeting several enzymes simultaneously, can quickly become computationally infeasible. There is a pressing need for systematic and efficient methodologies that leverage nonlinear dynamic models for strain design to address these challenges. We propose a comprehensive framework for rational strain design, offering robust design choices aimed at maintaining the desired phenotype of engineered strains in close proximity to that of the reference strain. To illustrate the features of the framework, we employed it for devising targets to overproduce anthranilate in E. coli shikimate metabolism. We identified multiple robust design targets through rigorous computational analysis, including eight targets previously validated experimentally. By doing so, we demonstrate the effectiveness of our approach in providing actionable insights for metabolic engineering endeavors. We expect this framework to play a crucial role in future design-build-test-learn cycles, providing high throughput, robust designs, and accelerating the production process in biotechnological applications.

MoDT1.9 (P1.9)

Non-Negative Universal Differential Equations with Applications in Systems Biology, pp. 42-47

Philipps, Maren; Körner, Antonia; Vanhoefer, Jakob; Pathirana, Dilan; Hasenauer, Jan

Universal differential equations (UDEs) leverage the respective advantages of mechanistic models and artificial neural networks and combine them into one dynamic model. However, these hybrid models can suffer from unrealistic solutions, such as negative values for biochemical quantities. We present non-negative UDE (nUDEs), a constrained UDE variant that guarantees non-negative values. Furthermore, we explore regularisation techniques to improve generalisation and interpretability of UDEs.

MoDT1.10 (P1.10)

Reconstructing Metabolic Interaction Networks in Microbial Communities, pp. 48-48

Sahin, Asli; Oftadeh, Omid; Vayena, Evangelia; Hatzimanikatis, Vassily

Found everywhere, from our gut to our water supply, microbial communities are vital to our health and the environment. These communities are influenced by metabolic interactions among their members, such as competition for nutrients or cross-feeding. However, the complexity of each organism's metabolic network within these communities makes it difficult to decipher these interactions. Computational tools can enable us to untangle this complexity and improve our understanding of the system.

Here, we present ReMIND (Oftadeh and Sahin et al., 2024), a computational framework to reconstruct the interaction networks in microbial communities based on the metabolic capabilities of individual organisms. To this end, we utilized genome-scale metabolic models and minimized the number of active exchange reactions for each organism, including uptakes and secretions. We generated all alternative Decomposed in silico Minimal Exchanges (DiMEs) and elucidated possible interaction networks based on various objective functions. We applied ReMIND to study the microbial interactions between the core members of the honeybee gut microbiome. Our results provide new perspectives on the evolutionary forces that shape these ecosystems and the trade-off between metabolite exchange and biomass yield. We systematically identified the most exchanged metabolites, highlighted metabolites mediating competition, and examined the effects of adding new members to a community. We envision that ReMIND will help characterize the metabolic capacity of individual members and elucidate metabolic interactions in diverse communities, thus guiding many applications from basic research to precision medicine and synthetic ecology.

MoDT1.11 (P1.11)

Improved Characterization of Multi-Sugar Growth Behavior by Model-Based Evaluation of Shake Flask Experiments, pp. 49-50

Valdeira Caetano, Ana Helena; Pably, Philipp; Sinner, Peter; Kager, Julian

This study characterizes Corynebacterium glutamicum growth on single and mixed sugars shake flasks experiments and evaluates the use of a simple mechanistic growth model to do so. The model shows better prediction capabilities over the traditionally used "simple" model-free methods to estimate the specific growth rates and yields, resulting in a 2.65-fold improvement of the average NRMSE of prediction.

MoDT1.12 (P1.12)

Extending a Synthetic Notch Morphogen Circuit Model to Construct 2D Cell Structures, pp. 51-56

Beyer, Amatus; Wagner, Vincent; Klingel, Viviane; Heymann, Michael; Radde, Nicole

Morphogenesis, the process of cells forming a defined shape, is central during embryonic development. Among other cues it involves diffusible signaling molecules, known as morphogens, and concentration-dependent cellular responses to these molecules. Recent advances in synthetic biology have enabled the isolated design and study of cellular systems that mimic morphogenesis. Here, we build on a system from Toda et al. (2020) that uses a synthetic Notch morphogen circuit to trigger and modulate gene expression. Following our vision of a model-based design of different cellular shapes and patterns, we present extensions of this framework based on the current synthetic Notch signaling capabilities described in the literature. We show first results of implementing morphogen-dependent proliferation as a particular example. The proliferation triggered by the morphogen modulates the steepness of the morphogen gradient, which directly translates to the signal readout. Furthermore, our modeling framework allows us to consider and design patterns in 2D that can be modulated by varying the size and location of the morphogen source and those of the interacting molecules, such as morphogen inhibitors. This bottom-up engineering approach opens up opportunities to better understand the underlying principles of morphogenesis and to design complex tissues with desired functions.

MoDT1.13 (P1.13)

Decoding Lactobacillus Bulgaricus Metabolism: Insights from a Dynamic Genome-Scale Model, pp. 57-58

Roudaut, Geoffrey; Moro, Francesco; Teusink, Bas; Balsa-Canto, Eva

Lactobacillus delbrueckii subsp. bulgaricus is one of the two indispensable bacteria constituting the yoghurt consortium. This work delves deeper into the dynamics of its metabolism in fermentation conditions. Our study combines a kinetic and a genome-scale model into a dynamic flux balance analysis to recover extracellular metabolite dynamics and pH effects on biomass growth, substrate uptake and by-product secretion. The dynamic model is based on experimental data and provides valuable insights into casein degradation and uptake by the cells.

MoDT1.14 (P1.14)

Correction of Microalgae Size Distribution Estimations Using Mie Scattering Theory, pp. 59-60

Busschaert, Michiel; Vermeire, Florence H.; Waldherr, Steffen

Estimating cell size distribution provides useful insights with respect to modelling, monitoring and control within a bioculture, as individual cell composition and metabolic rates may vary according to cell size. This size is related to scattering properties, which may be measured for a large number of cells using flow cytometry. Although, this relation may be characterized using reference particles of known size, differences in optical properties between these particles and the measured cells may influence cell size estimation accuracy. In this short paper, we propose an additional calibration step which accounts for differences in optical properties based on physics using Mie scattering theory.

MoDT1.15 (P1.15)

Towards a Genome-Scale Metabolic Model of Dunaliella Salina, pp. 61-66

Cunha, Emanuel; Sousa, Vitor; Vicente, António; Geada, Pedro; Dias, Oscar

Dunaliella salina is a green algae known for its ability to produce carotenoids. However, maximizing its production while achieving significant biomass yields remains challenging, which can be addressed through systems biology tools like genome-scale metabolic models. This work presents the first genome-scale metabolic model for D. salina, enabling an in silico analysis and optimization of β-carotene and lutein production. In silico simulations predict that reducing nitrate and phosphate availability increases the potential for carotenoid production. The flux scanning based on the enforced objective flux method was applied, allowing the identification of reactions that induce the cumulative production of both carotenoids and biomass

MoDT1.16 (P1.16)

A Multi-Omics Approach for Understanding Grape Metabolism Throughout Development, pp. 67-72

Sampaio, Marta; Rocha, Miguel; Dias, Oscar (presented by *Cunha, Emanuel*)

Multi-omics integration is a novel approach that combines data from different biomolecular levels, such as genes, proteins, and metabolites, to obtain a comprehensive view of the biological system. This approach is even more relevant for studying plants, as plant metabolism includes complex and interconnected mechanisms responsible for environmental adaptation. Plant

metabolism has also been studied using Genome-Scale Metabolic Models (GSMMs), which generate in silico phenotype predictions that can be integrated with experimental omics to improve data interpretability. In this work, transcriptomics and metabolomics data of grapes, and flux distributions predicted by GSMMs of V. vinifera were integrated using DIABLO to identify the relationships between genes, metabolites and reactions during grape development and potential biomarkers for each developmental stage. Malate, sucrose and glucose showed the highest correlations with genes and reactions and a high impact on the model's classifications of grape stage. The most contributing genes and reactions were more active in the green stage. This approach represents the first effort to integrate multi-omics and metabolic models for studying plant metabolism.

MoDT1.17 (P1.17)

Reconstructing and Analyzing the Experimentally-Supported Binary Protein-Protein Interaction Network of Moorella Thermoacetica, an Anaerobe of Industrial Interest, pp. 73-78

Savvopoulou, Vasiliki; Klapa, Maria

There has been a rapidly increasing industrial interest in developing optimized engineering solutions for CO_2 capture and subsequent conversion into biofuels and useful chemicals. The investigation of the non-photosynthetic CO_2 bioconversion has gained momentum in the field of metabolic engineering and industrial biotechnology in recent years, as an alternative to the biomass-based microbial processes. Acetogens are bacteria, which possess the particular ability of using catabolically the relevant Wood – Ljungdahl (W-L) pathway. The thermophilic obligatory anaerobe, *Moorella thermoacetica*, has been the model acetogen due to its small fully-sequenced genome. Furthermore, its metabolic network has been reconstructed and relevant metabolic boundaries have been determined. However, its protein-protein interaction (PPI) network remains unexplored. In fact, PPI networks have not been studied extensively in bacteria. On the other hand, multi-omic analyses are crucial to further our understanding of bacterial molecular physiology and regulation, and the integrated interpretation of omic datasets in the context of multi-level biomolecular networks is of great value and should be increasingly used in microbial research too. In this study, we extend the biomolecular analysis toolbox of *M. thermoacetica* by reconstructing a high-confidence experimentally-supported protein-protein interaction (PPI) network, based on (a) systematic literature curation, (b) comparative genomic analysis of the experimental binary PPI networks of *Bacillus subtilis*, an evolutionary adjacent microorganism, as well as the model-bacterium *Escherichia coli*, and (c)the functional PPI resource STRING. The PPI network was further analyzed for its topology and pathway enrichment, including links to the metabolic network. The acquired results supported the need to pay better attention to the elucidation of microbial PPI networks, especially of the extremophiles that have gained industrial interest.

MoDT1.18 (P1.18)

Investigating a Pilot-Scale Process Sustainability Integrating CO2 Capture with Its Bioconversion for Carbon Footprint Decrease of Lignite-Based Power Plants, pp. 79-79

Skouras, Eugene; Savvopoulou, Vasiliki; Aviziotis, Ioannis; Karagiannakis, Nicholas; Vroulias, Dionysios; Petsi, Anastasia; Dracopoulos, Vassilios; Ioannides, Theophilos; Zois, Ioannis; Klapa, Maria; Burganos, Vassilis

In this study, we investigated the sustainability of a process combining the use of carbon dioxide capture methods with the non-photosynthetic CO2 bioconversion into biofuels and chemicals/biologicals from extremophilic bacteria, which possess the capability to use CO2 as the main carbon source. The study integrates cutting-edge engineering technologies about CO2 capture and use into valuable chemicals, respectively, which have been traditionally optimized separately, while also representing two traditionally more distant engineering science domains. However, there is a high need to examine whether they can be successfully combined into a sustainable and efficient workflow at the laboratory and pilot-scale, having subsequently the possibility for further development to a more mature product. To this end, mathematical modeling of the specific sections of the integrated process individually and in combination was applied in order to predict the response and the boundaries of the system, taking into consideration the specifics of each module. We will present the modeling of a pilot-scale process, in which we took into consideration realistic input and output types and rates at the various parts of the process, using data from high CO2 emitting lignite-based power plants in Greece and the theoretically optimal conditions of CO2 capture technologies along with reported and experimentally produced data about the CO2 bioconversion from the strict anaerobe model-acetogen Moorella thermoacetica. Data about CO2 absorption and desorption conditions were provided by the involved collaborating groups. For the bioconversion, we considered mixotrophic (with glucose) microbial cultures at the conditions previously optimized for continuous cultures to decrease the needs for hydrogen availability. No previous investigation of the particular bioprocesses in sync with CO2 absorption/desorption units has been carried out to-date. Our data support the sustainability of such process, with the initial establishment cost appearing as the major expense. The study has been funded by NSRF 2014-2020 BIOMEK" (T1EΔK-00279)and HFRI Greece 2.0 CO2BION (#016103) projects and FORTH/ICE-HT internal funding.

MoDT1.19 (P1.19)

Analysis and Reduction of a Dynamic Model of Phage Attack Dynamics in Cheese-Making, pp. 80-80

Bou Habib, Michèle; BERNUAU, Emmanuel; Sánchez, Benjamín José; Vindeloev, Jannik; Swennen, Dominique; Trelea, Ioan-Cristian

Milk acidification is a key step in the cheese-making process. In the industry, bacteriophages can attack lactic acid bacteria (LAB), which are responsible for the conversion of lactose to lactic acid. In consequence, acidification can be reduced or even stopped, leading to a halt in the production and thus severe economic losses for cheese-makers. The goal of this study is to predict the dynamics of phage attack. To build a predictive model, acidification curves, i.e. pH measurements versus time, were generated for 48 different couples of initial LAB concentrations and phage titers. The acidification data showed that normal acidification takes place when the LAB concentration is high and phage titer is low. A dynamic mechanistic model was constructed and consisted of 5 ordinary differential equations for the state variables: lactose and lactic acid concentration, susceptible, and infected LAB concentration, and phage titer. The model was validated against experimental data. This model succeeded in predicting most of the phenomena taking place in the experiment. Important parameters and behaviors were deduced from simple and low-cost acidification measurements. The model simulates time evolution of phage and bacteria concentrations which are not measured routinely. Then, a theoretical analysis of the model was performed. New valuable parameters were derived and phage attack dynamics could be separated into three phases: contamination, spread, and discharge. A change of variables was done, and using the method of singular perturbations, these variables' evolutions in time were directly approximated. An explicit dynamic relationship between pH and the initial conditions was established. The model was successfully reduced, saving 84% of computational time. The model can be expanded to include different phages and bacteria species, and blends of both to mimic a typical cheese-making environment. The model can be used to raise awareness amongst cheese-makers on the importance of cleaning to avoid economic losses.

MoDT1.20 (P1.20)

Metabolomics in Systems Agrobiotechnology & Ecology for High Sensitivity Monitoring of Plant Physiology, pp. 81-81

Tooulakou, Georgia; Klapa, Maria

In agrobiotechnology, precision agriculture, nutrition and ecological research and practice, there is a need for accurate and sensitive tools for plant physiology monitoring along with furthering our understanding of the plant stress mechanisms. Both will (i) enable early diagnosis of critical perturbations and identify potential effective counteractions; (ii) help validate the quality and consistency of plant cultures and products; (iii) help understand the causes and evolution of ecosystem structure and function in response to environmental alterations, finding direct application in ecological restoration applications in response to damage caused

by climate change and pollution. Omic analyses in systems biology can help towards this direction, especially metabolomics as monitoring plant metabolism, the dynamic molecular level closest to the phenotype. In combination with (eco)physiological measurements and biomolecular network reconstruction and analysis, metabolomics can help in the development of standardized systems for plant physiology monitoring and control of plant growth environment. We present two applications of metabolomic analysis in systems biology as (1) crop and product quality monitoring and evaluation tool, and (2) ecological research tool for understanding the evolution of ecosystems in response to environmental changes. The two applications involve collaborative projects of our laboratory, two nationally-funded, one investigating the combined effect of high salinity and high CO2 on tomato crop (PHYTOALATOTITA) using metabolomics followed by a project investigating the metabolic differences between various Greek tomato varieties (NSRF 2014-2020 NTOMATOMICS, T2EΔK-01332) and one EU-funded project investigating the reponse of an amphibious plant to nutrient level changes and/or shading.

MoDT1.21 (P1.21)

Mutualistic Bacterial Relationships in Cheese Microbial Communities: Exploring Interactions through Kernel-Based Multi-Omics Data Integration, pp. 82-82

Mekuli, Rina; Briscik, Mitja; Landaud, Sophie; Déjean, Sébastien; Swennen, Dominique

The cheese ecosystem serves as a model environment to study the interactions that shape microbial communities and the physiology behind them. The aerobic nature of ripening bacteria and the low bioavailability of iron in milk demonstrate how iron can play an instrumental role in microbial relationships. B. aurantiacum and H. alvei, two important bacteria in the cheese industry, exhibit mutualistic behaviour. B. aurantiacum benefits from the (iron-chelating) siderophores synthesized by H. alvei, and in turn, H. alvei benefits from the proteolytic activity of B. aurantiacum. To gain an in-depth understanding of this exchange, multi-omics data were collected from bacteria cultivated in iron-rich and iron-poor environments, in monocultures and cocultures. Understanding cellular processes at transcriptome, proteome, and metabolome levels provides a comprehensive view of the subject. However, the integration of heterogeneous sources poses a significant challenge in systems biology. This complexity requires the use of ad hoc statistical methodologies, such as PLS-related or kernel-based methods, to unravel the relationships between the different datasets acquired on the same biological samples. These methods offer an ideal integration framework, particularly for multi-omics datasets where the number of variables is much larger than the number of samples. Furthermore, kernel-based algorithms such as Kernel principal component analysis are valuable tools to address the nonlinearity of biological sample spaces, potentially revealing interactions that classical linear methods may not detect. This study illustrates the practical application of a novel feature selection method we recently developed for kernel-based approaches. The method effectively identifies the key variables that characterize the iron-rich and iron-poor environments, in monocultures and cocultures.

MoDT1.22 (P1.22)

Model Predictive Control of Dissolved Oxygen Level in an Intermittent Fed-Batch Process, pp. 83-83

Pably, Philipp; Huusom, Jakob Kjøbsted; Kager, Julian

Bioprocess engineering tries to create the ideal physiological conditions for the organisms inside of a bioreactor to avoid byproduct formation, unwanted metabolic shifts or cell death. The dissolved oxygen (DO) level in the broth is a key process parameter and is manipulated by the stirring speed, the aeration flow rate and the partial pressure of oxygen. Commonly, simple cascaded PID control loops that act on the DO signal falling underneath a set threshold are deployed. However the inherent non-linear process dynamics of microbial cultivations pose difficulties for these control algorithms, even when extended through feedback linearization or gain scheduling as discussed by ˚Akesson and Hagander (1998). In the face of abrupt changes in nutrient additions, the DO signal will suddenly drop and eventually the purely reactive controller will not be able to avoid phases of oxygen limitation, as described by Kim et al. (2023). These problems can be observed in high throughput small-scale multi-reactor systems, where a scheduled pipetting robot adds the nutrients in form of bolus shots to the individual cultivations. The resulting oxygen limitations can affect the health and productivity of the organism, which calls for a more advanced control scheme. Model Predictive Control (MPC) emerges as a promising alternative to account for the non-linear process dynamics directly within the control loop. To enable this algorithm a process model is constructed by combining first principal mass balances, a simple cell growth kinetic and the kLA correlation proposed by Van't Riet (1979) to estimate the oxygen demand as well as the oxygen transfer rate in the reactor. The latter directly implements the stirring speed and the air gas flow, the two actuators of the control loop. The resulting process model is parameterized with laboratory-scale experiments combining online and offline signals. The MPC algorithm is then tested in-silico with different configurations for the objective function and compared to the performance of a tuned PID control.

MoDT1.23 (P1.23)

Machine Learning-Led Medium Optimization Uncovers High Salinity As an Enhancer for Biochemical Production of Flaviolin in P. Putida, pp. 84-84

Zournas, Apostolos; Incha, Matthew; Radivojevic, Tijana; Chung, Daniel; Garcia-Martin, Hector

Synthetic biology holds the promise of synthesizing valuable chemicals, but its progress is still hindered by a lack of predictive capabilities. Media optimization, a critical yet often overlooked process, is essential to achieve the titers, rates, and yields necessary for commercial viability. Predicting the optimal media is of significant practical importance for synthetic biology and metabolic engineering. This study presents a semi-automated robotic process that optimizes culture media through a recursive Design-Build-Test-Learn (DBTL) cycle, guided by an active learning machine learning algorithm (the Automated Recommendation Tool, ART) (Radivojević et al., 2020). By applying this process to the synthesis of the red pigment flaviolin in Pseudomonas putida (Incha et al., 2020), the study used ART to optimize the media. We achieved significant titer and yield increases. A tradeoff between increasing titer and yield was observed, controlled by glucose concentration. Surprising media components had a critical effect on final production. This study shows the effectiveness of machine learning-based approaches both in media optimization and in generating counterintuitive results.

19:30-21:00 ROOM CALYPSO

Poster Session I - Presentations + Wine & Cheese Buffet

Chair: Aleiferis, Spyridon Complexity Cybernetics SPPC

Program and Abstracts Tuesday September 10, 2024

09:00-11:10 TuAT1 Room NAFSIKA **General Session 3** – **Methods and Tools** *Session Chair: Steffen Waldherr, University of Vienna, Austria*
11:10-11:30 Coffee Break
11:30-12:30 TuBT1 Room NAFSIKA **Panel Discussion 2** – **Systems & Synthetic Biology: What about training, funding and publishing?** *(Moderator: Maria I. Klapa, FORTH/ICE-HT, Greece)* **Panelists:** *John Hancock, Co-leader of ELIXIR Systems Biology Community, U. of Ljubljana, Slovenia* *Jesus Pico, IFAC TC 8.4 Leader, Technical University of Valencia, Spain* *Ioannis (Yannis) Androulakis, Rutgers University, USA* *Thomas C. Collin, Frontiers in Systems Biology* *Ashti Shah, School of Medicine, University of Pittsburgh, USA*
12:30-13:15 TuCT1 Room NAFSIKA **POSTER SESSION II - Pitches** *Chair: Yadira Boada, Universitat Politécnica de València, Spain*
13:15-15:00 TuDT1 Room CALYPSO (Presentations) + Veranda PERGOLA (Buffet) **POSTER SESSION II - Presentations + Light Lunch Buffet**
15:00-16:20 TuET1 Room NAFSIKA **General Session 4** – **Control in Biology** *Session Chair: Jesus Pico, Universitat Politécnica de València, Spain*
16:20-17:00 Coffee Break
17:00-18:00 TuFT1 Room NAFSIKA **General Session 4** – **Control in Biology** *Session Chair: Jesus Pico, Universitat Politécnica de València, Spain*
18:00-19:00 TuGT1 Room NAFSIKA **Keynote Lecture II** *Session Chair: John Hancock, U. of Ljubljana, Slovenia* **Two Decades of BioModels: Promoting FAIR Sharing and Reproducibility of Computational Models in the Life Sciences** *Sheriff Malik Rahuman, European Bioinformatics Institute (EBI), UK*
19:30-23:00 **Guided Tour of the Old Town of Corfu (Unesco Monument) + Gala Dinner in Corfu town**

Technical Program for Tuesday September 10, 2024

TuAT1	Room NAFSIKA
Session 3: Methods and Tools (Regular Session)	
Chair: Waldherr, Steffen	University of Vienna
09:00-09:30	TuAT1.1 (Invited Lecture 5)

*ASIMOV: Intelligent Design of Living Systems**

Haddock, Traci

In this talk, the Director of Community of Asimov delves into the cutting-edge fusion of mammalian synthetic biology, computer-aided design, and machine learning. The presentation highlights how Asimov is pioneering the intelligent design and programming of living cells, revolutionizing the development of biologics and gene therapies. Through a multidisciplinary approach, the speaker will explore the innovative tools and methodologies being used to advance the design and manufacture of next-generation therapeutics.

09:30-09:50	TuAT1.2 (OP8)

Generative Machine Learning Methods for Parameterizing Nonlinear Dynamic Models of Cellular Metabolism, pp. 85-85

Miskovic, Ljubisa; Choudhury, Subhan; Hatzimanikatis, Vassily

The use of generative machine learning methods to parameterize nonlinear dynamic models has the potential to revolutionize our understanding of the complex metabolic processes that occur within cells. Dynamic models provide the most comprehensive mathematical portrayal of metabolism, distinguishing themselves by their unique ability to amalgamate omics and physicochemical data, allowing for effective data integration. We recently introduced REKINDLE (REconstruction of KINetic models using Deep Learning)1 to democratize access to large-scale nonlinear dynamic models. Leveraging neural networks' predictive capabilities, REKINDLE significantly reduces the substantial computational resources required by traditional kinetic modeling techniques. The framework's adaptability for studying multiple phenotypes and

large cohorts is facilitated because neural networks, which parameterize kinetic models for one study, can be retrained for other studies using only a few data points. While REKINDLE efficiently generates dynamic models, it depends on existing kinetic modeling methods to produce data for training neural networks. We recently developed RENAISSANCE (REconstruction of dyNAmIc models through Stratified Sampling using Artificial Neural networks and Concepts of Evolution strategies)2 to overcome this limitation without compromising model construction efficiency. This high-throughput generative machine learning framework parameterizes biologically relevant dynamic models efficiently without requiring training data. The dynamic models yielded by the proposed frameworks prove valuable for studying metabolic processes, as we will demonstrate through several case studies. We will then present our latest efforts in using machine learning for tuning different model properties. The presented methods pave the venue for conducting dynamic studies of metabolism for diverse health and biotechnology applications in a high-throughput manner.

[1] Choudhury et al., Reconstructing Kinetic Models for Dynamical Studies of Metabolism using Generative Adversarial Networks. Nature Machine Intelligence 4, pages 710–719 (2022) [2] Choudhury et al., Generative machine learning produces kinetic models that accurately characterize intracellular metabolic states. bioRxiv, (2023)

09:50-10:10 TuAT1.3 (OP9)

Coarse-Grained Models: Basics and Applications in Systems Biology and Bio-Process Engineerin, pp. 86-86

Kremling, Andreas

Understanding complex systems, whether in technical or non-technical disciplines, heavily relies on mathematical modeling. This is particularly evident in the life sciences, notably in systems biology, where mathematical modeling serves as a formal tool for grasping the complexities of a system. Systems theory provides a framework for constructing models with various dimensions. One dimension involves the level of detail in the model, ranging from simple qualitative interaction networks to comprehensive, mass-conservative quantitative models that detail processes within cells and their fluctuating environments. Another dimension pertains to whether the model represents an average cell or individual cells within an environment. Modeling individual cells necessitates sophisticated approaches, such as employing population balance equations or adopting an ensemble modeling approach. Additional dimensions include whether the system is static or dynamic, and if the model requires structural elements, like an objective function, to explore the potentially infinite solution space.

In recent years, coarse-grained modeling approaches have gained popularity, particularly in proteome allocation studies, revealing interesting results that demonstrate how bacteria like <i>Escherichia coli<i> optimally distribute their resources. However, some published models lack strict mass conservation, complicating their application in bio-process design. This contribution presents theoretical basics for coarse-grained models incorporating metabolic networks and multiple compartments, with a focus on steady-state behavior. These models necessitate an objective function since the number of equations is insufficient to determine all state variables. To mimic growth and production behavior in large bioreactors, a single-cell modeling strategy for a combined stirred tank/plug flow system is proposed, enabling the recording of time-course data for single cells and, based on this, the establishment of distributions of individual cell components. In this approach, to reduce simulation time, the objective function was replaced by a correlation of state variables.

10:10-10:30 TuAT1.4 (OP10)

Reducing Genome-Scale Models Using Network Topology Information and Transcriptomics, pp. 87-88

Troitiño-Jordedo, Diego; Mansouri, Anis; Minebois, Romain; Querol, Amparo; Remondini, Daniel; Balsa-Canto, Eva

A Genome-scale model (GEM) is a mathematical representation of the metabolism of a given organism based on its biochemical, genomic, and physiological information. GEMs aim to include all reactions suggested by the genome annotation plus transport reactions. However, not all of them will be active under specific conditions. We propose a new method integrating network topology information and transcriptomic data to obtain reduced representations. We consider the case of yeast fermentation and compare our results with the ones obtained by standard alternatives. Our method results in reduced GEMS with plausible biological behaviour.

10:30-10:50 TuAT1.5 (OP11)

Adapting Tree Algorithms for Partial Enumeration of Extreme Pathways Sets, pp. 89-94

Mores, Wannes; Bhonsale, Satyajeet; Logist, Filip; Van Impe, Jan F.M.

Analysis of metabolic networks through characterising flux vectors such as Elementary Flux Modes and Extreme Pathways has shown to be valuable in many application within systems biology. However, their application is still limited to medium-scale metabolic networks due to the combinatorial explosion of the set size. Enumeration of the full set in genome-scale metabolic networks remains impossible, but few techniques exist for partial enumeration. Currently, an adapted version of the Canonical Basis Approach for generation of Extreme Pathways has allowed partial enumeration with good sampling quality through a filter. However, computational efficiency currently limits its application, especially when moving towards larger networks. One approach to increase this efficiency significantly is through candidate narrowing based on bit pattern trees. Here, many of the candidate modes are removed every iteration based on their ability to pass a rank test. However, the depth of the trees should be adapted based on the filter setting and the current amount of candidates to process. In this work, a novel algorithm is presented using candidate narrowing in a stochastic partial enumeration of Extreme Pathways. A case study for the central carbon metabolism of Escherichia coli showcases the adaptive tree depth and the overall performance increase for different settings.

10:50-11:10 TuAT1.6 (OP12)

Low-Dimensional Representations of Genome-Scale Metabolism, pp. 95-100

Cain, Samuel; Merzbacher, Charlotte; Oyarzún, Diego A.

Cellular metabolism is a highly interconnected network with thousands of reactions that convert nutrients into the molecular building blocks of life. Metabolic connectivity varies greatly with cellular context and environmental conditions, and it remains a challenge to compare genome-scale metabolism across cell types because of the high dimensionality of the reaction flux space. Here, we employ self-supervised learning and genome-scale metabolic models to compress the flux space into low-dimensional representations that preserve structure across cell types. We trained variational autoencoders (VAEs) on large fluxomic data ($N=800,000$) sampled from patient-derived models for various cancer cell types. The VAE embeddings have an improved ability to distinguish cell types than the uncompressed fluxomic data, and sufficient predictive power to classify cell types with high accuracy. We tested the ability of these classifiers to assign cell type identities to unlabelled patient-derived metabolic models not employed during VAE training. We further employed the pre-trained VAE to embed another 38 cell types and trained multilabel classifiers that display promising generalization performance. Our approach distils the metabolic space into a semantically rich vector that can be used as a foundation for predictive modelling, clustering or comparing metabolic capabilities across organisms.

11:10-11:30 Room NAFSIKA

Coffee Break

TuBT1 Room NAFSIKA

Panel Discussion II: Systems & Synthetic Biology: What about training, funding and publishing?

Moderator: Maria I. Klapa FORTH/ICE-HT, Greece

11:30-12:30

Panelists:

John, Hancock, Co-leader of ELIXIR Systems Biology Community, U. of Ljubljana, Slovenia

Jesus, Pico, IFAC TC 8.4 Leader, Technical University of Valencia, Spain

Androulakis, Ioannis (Yannis), Rutgers University, USA

Collin, Thomas C., Frontiers in Systems Biology

Shah, Ashti, School of Medicine, University of Pittsburgh, USA

12:30-13:15 **TuCT1**

Poster Session II - Pitches NAFSIKA

Chair: Boada, Yadira Techical University of Valencia

TuCT1.1 (P2.1)

Feasibility of Gene Regulatory Network Inference under Different Noise Conditions, pp. 101-106

Michael, Saint-Antoine; Singh, Abhyudai

One of the most difficult and pressing problems in computational cell biology is the inference of gene regulatory network structure from transcriptomic data. Although this topic has been widely studied for more than a decade, it is still unclear how well these methods work and how their performance differs under different conditions. We analyze the feasibility of network inference from mRNA abundance data using simulations of gene regulatory interactions, considering both intrinsic and extrinsic noise in the process of gene expression. We find that under conditions of only intrinsic noise in gene expression, the correlation between mRNA levels of genes in an activation relationship is quite low, suggesting that the task of network inference from transcriptomic data is very difficult under these conditions. By contrast, extrinsic noise affecting the process of gene expression, which could come from an upstream regulator, external stimulus, or change in the cell state, results in higher correlation between mRNA levels of these genes, potentially making the task of network inference from mRNA data more feasible. Lastly, we analyze the problem of false positives between genes that have no direct interaction but share a common upstream regulator, and explore a strategy for distinguishing between these false positives and true interactions based on noise profiles of mRNA expression levels.

TuCT1.2 (P2.2)

Bioinformatic Workflow for Mass Spectrometry-Based Metabolomics of Yeast: State of Art and Perspectives, pp. 107-107

De Martino, Luca; Mastrorocco, Fabrizio; MUSICCO, CLARA; Pesole, Graziano; Picardi, Ernesto; Klapa, Maria; Giannattasio, Sergio

Background. Metabolomics addresses the high-throughput study of metabolites, which act as reactants and products of metabolic reactions in biological systems. The metabolome reflects the complex association between genome and environment, arising from interactions between different biological information layers including genome, transcriptome, and proteome. Advanced analytical techniques enable untargeted metabolomics, facilitating the identification of the whole complement of metabolites in a biological system, which remains still far from being achieved. Yeast is a well-established model for studying the molecular and systems biology of higher eukaryotes due to its similarities to humans in cellular components and processes. We carried out integration of differential metabolomics and transcriptomics data of 휌0 versus 휌+ yeast cells to evaluate bioinformatic tools for integrative omics analysis and to gain insights into metabolic reconfiguration of cells with dysfunctional mitochondria.

Methods. Orbitrap Fusion™ Tribrid™ HRMS platform (Thermo Fisher Scientific) was used for untargeted metabolomics analysis. A survey of open-source tools for annotation, interpretation and integration of untargeted metabolomics data was made to compare their performance with that of Compound Discoverer™ software (Thermo Fisher Scientific). 휌0/휌+ differential metabolomics data were integrated with published differential transcriptomics data in a standard knowledge-based manner as well as using open-source tools.

Results. The use of Compound Discoverer™ and a knowledge-based method for integration of metabolomics and transcriptomics data allowed identification of certain metabolic pathways altered in respiratory deficient ρ0 cells. These results were compared with those obtained using a fully computer-aided integration method through open-source bioinformatics tools for annotation and integration, including SIRIUS (Dührkop K., et al., Nat Methods, 2019) and MetaboAnalyst 6.0 (Pang Z. et al., Nucleic Acids Research, 2024) which was identified as the best for improving metabolite annotation and performing multi-omics data integration. Although the altered metabolic pathways are comparable, the knowledge-based method still provides more specific information regarding pathways alteration.

Conclusion. Establishing adaptable, standardized workflows aligned with FAIR principles is critical. However, a universally accepted metabolic model for yeast is lacking and standardization issues persist, requiring the development of an improved yeast metabolic model, integrated with the other molecular levels of cellular function in the context of integrative systems biology studies. This will enhance our understanding of yeast metabolism and enable broader applications, easily translated to higher organisms like humans.

Acknowledgements. Luca De Martino is a PhD student enrolled in the National PhD in Artificial Intelligence, XXXVIII cycle, course on Health and life sciences, organized by Università Campus Bio-Medico, Rome. Fabrizio Mastrorocco is funded by ELIXIRxNextGenerationIT PNRR Project (IR0000010). All analyses are currently supported by the ELIXIR infrastructure.

TuCT1.3 (P2.3)

Metabolic Kinetic Modeling Unveils Pivotal Enzymes in Cancer Cell Metabolism, pp. 108-108

Toumpe, Ilias; Masid Barcon, Maria; Narayanan, Bharath; Miskovic, Ljubisa; Hatzimanikatis, Vassily

The metabolic rewiring observed in cancer cells, including elevated aerobic glycolysis and alterations in mitochondrial metabolism, have attracted considerable interest in cancer research due to their pivotal role in supporting the rapid proliferation and survival of cancer cells. Understanding the metabolic vulnerabilities of cancer cells allows for developing targeted therapies to disrupt tumor growth. In this study, we report a large-scale dynamic model of cancer metabolism offering the possibility to identify tumor-specific and patient-specific drug targets. To achieve this objective, we started with a representative stoichiometric model of ovarian cancer metabolism produced using the redHUMAN workflow (Masid et al., 2020). This model comprises over 2300 reactions and more than 950 metabolites. We then integrated transcriptomic, fluxomic, metabolomics, and thermodynamic data using REMI (Pandey et al., 2019) to compute the steady-state values of metabolite concentrations and metabolic fluxes for the studied phenotype. Building upon the devised stoichiometric model, we constructed a large-scale kinetic model with more than 700 differential equations and over 9500 kinetic parameters using the ORACLE framework (Miskovic & Hatzimanikatis, 2010) and the SKiMpy toolbox (Weilandt et al., 2022). The devised models allow us to simulate dynamic metabolic responses with physiologically

relevant timeframes, providing diverse possibilities for investigating drug metabolism in cancer cells. They also allow us to identify the enzymes governing cancer cell proliferation. Our analysis uncovers that enzymes originating in oxidative phosphorylation, nucleotide, and lipid metabolism pathways exert the most significant impact on cancer cell growth, aligning closely with experimental evidence. We further conducted dynamic simulations uncovering the transient effects of drug administration on the entire cancer cell metabolic network. The relative decrease in cancer proliferation is estimated along with other metabolic components such as the adenylate pool distribution, nucleotides, and the oxygen consumption rate. Overall, our large-scale kinetic models of cancer metabolism unravel crucial insights into the metabolic vulnerabilities of cancer cells and offer unparalleled opportunities for investigating cancer metabolism in depth. We anticipated that this work would significantly advance our understanding of this complex system.

TuCT1.4 (P2.4)

Foliar Uptake Models for Biocides: Testing Practical Identifiability of Diffusion-Based Models, pp. 109-114

Sangoi, Enrico; Cattani, Federica; Padia, Faheem; Galvanin, Federico

With the expanding global population and diminishing resources, the imperative of ensuring sufficient food production becomes increasingly urgent. It is pivotal to develop safer biocides to enhance crop yields and address the escalating demands for food. Mathematical models are essential for understanding and characterizing the dynamic behaviour of complex biological systems. This work focuses on the development and statistical validation of a model for the description of biocide uptake through the leaves of plants. The systematic modelling strategy applied follows the steps: 1) formulation of candidate models; 2) conduction of identifiability tests to verify that model parameters can be estimated from observations; 3) selection of the best model based on its statistical performance in representing the experimental observations; 4) design of experiments for improving the precision of parameter estimates from data; 5) statistical validation of the final model. This paper presents a diffusion-based model for foliar uptake and a study on the practical identifiability of the model parameters (steps 1 and 2 of the procedure outlined). These results will guide further model-driven experimentation in the context of foliar uptake of pesticides.

TuCT1.5 (P2.5)

Ratiometric Control of Two Microbial Populations in a Dual Chamber Bioreactor, pp. 115-115

Brancato, Sara Maria; Salzano, Davide; Fiore, Davide; Russo, Giovanni; di Bernardo, Mario

Microbial consortia, comprising multiple interacting populations, hold immense potential for various biotechnological applications due to their enhanced survival fitness and efficiency. However, ensuring stable coexistence among heterogeneous populations poses a significant challenge, particularly in the face of varying growth rates and metabolic loads, especially when the species are not complementary, i.e. one species always outgrowing the other when left uncontrolled. Here, we present a novel control architecture based on the use of two bioreactors in which the slower species is separately grown and can be added to the main mixing chamber. By employing a dilution rate control strategy in combination with a reservoir bioreactor hosting the slower-growing population alone, we demonstrate robust coexistence between the populations. We develop mathematical models to describe the growth dynamics and design open-loop and closed-loop controllers to regulate the consortium's properties. We validate in silico the effectiveness and robustness of the proposed approach using models parameterized onto real experiments. The numerical results illustrate the potential applicability of our approach across diverse microbial strains without the need for any genetic modifications. Our proposed platform provides a promising solution for creating functional microbial consortia capable of reliably performing desired tasks in biotechnological settings.

TuCT1.6 (P2.6)

A Systematic Mixed Integer Linear Programming Approach for the Solution of Large-Scale Metabolism and Protein Expression (ME-) Models, pp. 116-116

Oftadeh, Omid; Hatzimanikatis, Vassily

One of the current most accurate models of biological systems includes metabolism and expression (ME-models), and Expression and Thermodynamics FLux (ETFL) is one such formulation that efficiently integrates RNA and protein synthesis with traditional genome-scale metabolic models. However, ETFL is so far only applicable for E. coli. To therefore adapt this ME-model for Saccharomyces cerevisiae, we herein developed yETFL. To do this, we augmented the original formulation with additional considerations for biomass composition, the compartmentalized cellular expression system, and the energetic costs of biological processes. We demonstrated the predictive ability of yETFL to capture maximum growth rate, essential genes, and the phenotype of overflow metabolism. Using externally available and in-house approaches, we developed sampling methods for ME-models to systematically obtain different possible distributions of fluxes and concentrations and meet the challenge of variability in the solutions space. We also expanded the application of ME-models to simulate recombinant organisms by capturing the plasmid burden. The allocation of cellular resources for plasmid-related activities, including plasmid replication and gene expression, exerts a burden on the cellular biosynthetic machinery, which results in a reduced growth rate. Understanding the plasmid burden at the molecular and mechanistic level will be important for synthetic biology and metabolic engineering. We used ETFL to capture the plasmid burden in Escherichia coli. Our expanded formulation allows efficient computation of the ME-models, and it is ideal when we want to use sensitivity analyses for deciphering the underlying mechanisms of complex cellular phenotypes. We first demonstrated that the ME-models could capture the experimental observations of decreased growth rate due to the increase in the copy number. We also showed that the plasmid replication burden is negligible compared with the burden caused by the plasmid gene expression. Finally, we explored the trade-off between biomass yield and product yield to find the optimal plasmid copy number.

TuCT1.7 (P2.7)

Robust Parameter Estimation and Identifiability Analysis with Hybrid Neural ODEs in Computational Biology, pp. 117-118

Giampiccolo, Stefano; Reali, Federico; Iacca, Giovanni; Marchetti, Luca

Neural Ordinary Differential Equations (NODEs) [1] offer a promising data-driven approach for modeling dynamical systems in computational biology. By integrating NODEs with mechanistic knowledge, computational models can be developed without a comprehensive understanding of the underlying biology, substituting areas lacking mechanistic descriptions with neural networks [2]. However, mechanistic parameter estimation in such hybrid scenarios is a challenging task, and, to the best of our knowledge, a method has yet to be proposed for analyzing the parameter identifiability in this context. Here we present an end-to-end pipeline for mechanistic parameter estimation and identifiability analysis in hybrid NODE models based on the Julia SciML framework [2]. The pipeline consists of four steps:

Step 1. Hyperparameter tuning and global exploration of the parameter search space using Bayesian optimization.

Step 2. Full training of the hybrid model with the Adam algorithm [3].

Step 3. A posteriori assessment of local identifiability of mechanistic parameters with an ad hoc variant of the eigenvalue method.

Step 4. Computation of asymptotic confidence intervals for mechanistic parameter estimates using the Fisher Information Matrix.

The pipeline has been tested in various in-silico scenarios of increasing complexity, supposing to lack portions of mechanistic knowledge in three models acknowledged as benchmarks in Computational Biology: we assume to ignore the interaction terms in the Lotka-Volterra model [4], and to have a completely missing equation in the cell apoptosis model [5] and in the yeast glycolysis model [6]. In silico observation datasets were generated to mimic real-world conditions, incorporating partially observable system variables and noisy measurement (zero mean Gaussian noise is added to each time series with SD equal to 5% of the data min-max variation). The pipeline successfully assesses the non-identifiability of parameters in the Lotka-Volterra test case, where the neural network can compensate for changes in the estimates of mechanistic parameters. In the cell-apoptosis test case, the pipeline correctly assesses the non-identifiability of three parameters while estimating four others (mean relative error among parameters less than 5%). In the glycolytic test case, 13 identifiable model parameters are correctly estimated (mean relative error among parameters less 25%).

The results demonstrate the reliability of the proposed pipeline in realistic scenarios where only small datasets are available, providing noisy observations for a limited number of system variables.

TuCT1.8 (P2.8)

From Genes to Metabolites to Diseases: A Multiomics Analysis of Tributyltin-Exposed Adipocytes and the Link to Metabolic Syndrome, pp. 119-120

Schultz, Dayna; Frydas, Ilias; Papaioannou, Nafsika; Papageorgiou, Thanasis; Gabriel, Catherine; Karakitsios, Spyros; Sarigiannis, Dimosthenis

Metabolic syndrome is a cluster of frequently co-occurring conditions linked to various health outcomes, increasingly attributed to exposure to endocrine-disrupting chemicals (EDCs). Specifically, EDCs may affect the normal development and function of adipose tissue, once considered an inert storage depot. However, mounting evidence suggests that it is a complex and metabolically active organ with a considerable influence on the regulation of metabolism and energy homeostasis. To explore relevant effects of EDCs, Simpson-Golabi-Behmel syndrome (SGBS) pre-adipocytes were exposed to tributyltin (TBT), a known lipogenic substance, to map the omics signature associated with metabolite and transcript dysregulation. SGBS pre-adipocytes were grown to near confluence and incubated in differentiation medium for four days, followed by cultivation in maintenance medium for six days. The differentiation medium of TBT-exposed cells was additionally supplemented with 25nM TBT during the initial four days. Cells were harvested at day 10 of differentiation and TBT-exposed and differentiated controls were compared. Samples for untargeted metabolomics were analyzed using Reversed Phase (RP) and Hydrophilic Interaction (HILIC) Liquid Chromatography in positive and negative ionization modes. Transcriptomics analysis was performed using Agilent microarrays to determine differentially expressed genes (DEGs) between treatment groups. Data preprocessing, batch correction, and statistical analyses were conducted in R using xcms, IPO, PMCMRplus, and xMSannotator packages for metabolomics, and limma for transcriptomics. An integrated omics analysis pipeline was employed, using univariate and multivariate approaches in mixOmics and MetaboAnalystR, aimed at enhancing the depth of understanding of multiomics mechanisms. This approach highlights both individual molecular changes and their integrated effects on cellular pathways. Across all analyses, perturbations in pathways linked to metabolic dysfunction, including dyslipidemia, obesity, and inflammation, were identified. The consistent identification of key features and shared perturbed pathways provides a foundation for further mechanistic investigations and potentially informs strategies for mitigating the adverse effects of exposures to metabolism-disrupting chemicals. Future studies will delve deeper into the adipocyte 'ome', seeking indications of susceptibility or early warning signs specific to health outcomes such as metabolic syndrome.

TuCT1.9 (P2.9)

Modeling Principles for a Physiology-Based Whole-Body Model of Human Metabolism, pp. 121-126

Blicher, Laura Hjort; Carstensen, Peter Emil; Bendsen, Jacob; Lindén, Henrik; Kristensen, Kim; Hald, Bjørn Olav; Jorgensen, John Bagterp

Physiological whole-body models are valuable tools for the development of novel drugs where understanding the system aspects is important. This paper presents a generalized model that encapsulates the structure and flow of whole-body human physiology. The model contains vascular, interstitial, and cellular subcompartments for each organ. Scaling of volumes and blood flows is described to allow for investigation across populations or specific patient groups. The model equations and the corresponding parameters are presented along with a catalog of functions that can be used to define the organ transport model and the biochemical reaction model. A simple example illustrates the procedure.

TuCT1.10 (P2.10)

Computational Modelling of Host-Parasite Metabolic Interactions to Guide Host-Directed Therapies, pp. 127-127

Joly, Denis Alain Henri Lucien; Masid Barcon, Maria; Maurizio, Marina; Woods, Kerry; Caldelari, Reto; Doench, John G.; Naguleswaran, Arunasalam; González Fernández, Martín; Zemp, Jonas; Borteele, Mélanie; Heussler, Volker; Rottenberg, Sven; Olias, Philipp; Hatzimanikatis, Vassily

Apicomplexan parasites, which include the causative agents of important diseases such as malaria, toxoplasmosis, and theileriosis, pose a major challenge to global health efforts. Combatting these diseases necessitates a comprehensive understanding of the complex metabolic interplay between the parasites and their host cells.

This work presents a computational framework to study the metabolic interactions between the liver-stage schizont of Plasmodium falciparum and primary Human hepatocytes. The novelty of our methodology lies in the computational efficiency of the concept of "parasitosomes" developed in this work. Parasitosomes are stoichiometrically balanced equations, each representing a distinct parasite metabolic state within the host environment. As such, they outline the diverse metabolic strategies employed by the parasite to assimilate nutrients from and release by-products back into the host's cytosol.

We validated our computational in silico gene essentiality predictions empirically by conducting comprehensive genome wide CRISPR/Cas9 knockout screens. These screens targeted bovine macrophages infected with Theileria annulata schizonts and enabled the identification of host genes indispensable for the parasite's survival but expendable for the host's viability. Such genes hold significant promise as targets for developing innovative therapeutic interventions.

Our comprehensive analysis reveals metabolic vulnerabilities shared by both Plasmodium falciparum and Theileria annulata, identified through computational simulations and experimental validations. These insights suggest promising strategies for targeting essential host metabolic pathways that potentially halt parasite development. Significantly, our findings highlight the crucial role of host cell metabolism in the life cycles of these parasites. This understanding opens new research avenues into the specific metabolic processes that sustain parasitic infections, moving beyond traditional treatment paradigms towards host-directed therapies.

TuCT1.11 (P2.11)

A Whole-Body Mathematical Model of Cholesterol Metabolism and Transport, pp. 128-133

Carstensen, Peter Emil; Bendsen, Jacob; Blicher, Laura Hjort; Kristensen, Kim; Jorgensen, John Bagterp

Cardiovascular diseases are the leading cause of death. Increased levels of plasma cholesterol are consistently associated with an increased risk of cardiovascular disease. As a result, it is imperative that studies are conducted to determine the best course of action to reduce whole-body cholesterol levels. A whole-body mathematical model for cholesterol metabolism and transport is proposed. The model can simulate the effects of lipid-lowering drugs like statins and anti-PCSK9. The model is based on ordinary differential equations and kinetic functions. It has been validated against literature data. It offers a versatile platform for designing personalized interventions for cardiovascular health management.

TuCT1.12 (P2.12)

Integrative Multi-Omics Approach: A Bioinformatics Workflow for Analyzing and Interpreting Transcriptomics and Metabolomics Data, pp. 134-135

Papaioannou, Nafsika; Papageorgiou, Thanasis; Schultz, Dayna; Dallas, Ioannis; Frydas, Ilias; Gabriel, Catherine; Karakitsios, Spyros; Anesti, Ourania; Sarigiannis, Dimosthenis

This study introduces a workflow within the R/Bioconductor framework for integrating and interpreting jointly transcriptomics and metabolomics data. The integrative bioinformatics workflow was demonstrated on HepaRG cells exposed to Di(2-ethylhexyl) phthalate. It covers sample preparation, data acquisition, individual omics data analysis, and multi-omics integration, addressing the need for algorithms that unify data from various biological "omes" to support knowledge discovery.

For transcriptomic analysis, the One-Color Microarray-Based Gene Expression Analysis Protocol was followed, ensuring optimal microarray results. Untargeted metabolomics analysis was performed using an LC-QTOF-HRMS system using reversed-phase and hydrophilic interaction liquid chromatography in positive and negative ionization modes. Transcriptomics raw data were exported as .txt files and imported into R. In R, data were analyzed using the limma package with built-in analyses specific for One-Color Agilent microarray data. Untargeted metabolomics data were processed using Bioconductor software packages (e.g. XCMS, IPO, and CAMERA). The Kruskal-Wallis test was applied after multi-filtering, normalization, scaling, log transformation, and batch effects correction, to detect differentially expressed features (DEF). DEF were annotated using online and in-house compound databases.

The multi-omics workflow is based on the MetaboAnalystR and MixOmics R packages, incorporating multivariate and joint pathway analysis. Integration of bioinformatics approaches, including network analysis, KEGG Mapper, Pathvisio, and Reactome, was employed for additional mapping. Multi-omics pathway analysis resulted in dysregulated pathways related to amino acids and lipid metabolism, that have been linked with downstream effects such as developmental neurotoxicity, endocrine and metabolic dysfunction.

In conclusion, the presented multi-omics workflow in R provides a valuable tool for identifying potential biomarkers associated with the toxicity mechanisms of investigated pollutants. The integration and interpretation of omics data contributes to a mechanistic understanding of underlying processes, crucial for translating findings into risk assessments.

TuCT1.13 (P2.13)

Estimating the Frequency Response of Zebrafish During Target Tracking, pp. 136-137

Anilmak, Sumeyye; Uyanik, Ismail

Animals are in a dynamic closed loop with their environment while performing their daily tasks. They perceive the world using the information they receive through various sensory organs in their bodies and react to the environment via various motor functions. Identifying the dynamics governing these input—output behaviors is critical to understand the underlying mechanisms adopted by the central nervous system (CNS) while controlling the body. In this study, we worked on identifying the dynamics of target tracking in zebrafish during their natural rheotaxis behavior. We developed a swim tunnel for the zebrafish to perform positive rheotaxis in a controlled environment. We then placed a multisensory obstacle that obscure the flow in a certain region. Zebrafish tracked moment-to-moment movements of this obstacle to remain within a low-gradient regime in the test area. We experimented with N=5 fish and spanned a frequency range of 0-1 Hz. We estimated the frequency response functions of the zebrafish while the fish tracks the movements of the obstacle during rheotaxis.

TuCT1.14 (P2.14)

Metabolic Modelling Reveals Key Pathways in COVID-19 in an Effort to Drive Drug Purposing, pp. 138-143

Oliveira, Alexandre; Rocha, Miguel; Dias, Oscar

Since the onset of the COVID-19 pandemic, there has been a pressing need for innovative drugs tackling this disease. In this context, this study aimed to develop context-specific metabolic models using transcriptomics data to uncover significant flux changes and drive drug repurposing. Differential flux analyses revealed significant flux alterations, particularly in fatty acid metabolism, with notable changes observed in cholesterol, retinol, arachidonic acid, and carnitine pathways. Drug targeting results primarily focused on impairing cholesterol biosynthesis. Overall, this work elucidated relevant interactions, highlighting the relevance of specific metabolic pathways in the infection process, which could be leveraged for potential novel treatments.

TuCT1.15 (P2.15)

Mini-Bioreactor for Parts Characterization of a Biological Circuit: Absorbance and Fluorescence Measurement Calibration, and Online Growth Rate Estimation, pp. 144-149

Díaz-Iza, Harold José; Arboleda-Garcia, Mario Andres; Boada, Yadira; Vignoni, Alejandro; Picó, Jesús

Synthetic Biology, like many other disciplines, is progressing every day. This progress has created the necessity to develop devices for measuring parameters and variables in order to characterize different aspects of genetic circuits. In the market, we can find many devices that fulfill this purpose. One of these devices is Chi.Bio, an open-source mini-bioreactor platform. The platform Chi.Bio allows us to measure process variables, such as fluorescence and absorbance, using its different sensors. Thus, it is necessary to develop protocols and procedures for calibrating data measurements from the Chi.Bio to increase the usability and interpretability of models and estimated parameters of a genetic circuit. Here, we propose a set of protocols and calibration procedures to obtain measurements of fluorescent E. coli cells in Molecules of Equivalent Fluorescein (MEFL) per cell for GFP constructs and we present an implementation of a second-order sliding mode observer to estimate the growth rate of E. coli cells in batch mode of Chi.Bio. The results show that calibrated measures are fundamental for getting reliable values to characterize genetic circuits in Synthetic Biology

TuCT1.16 (P2.16)

Cooperative Reactions for Designing Robust Biomolecular Circuits Exhibiting Homeostatic Behavior, pp. 150-151

Procopio, Anna; Montefusco, Francesco; Cortese, Nicola; Ariola, Marco; Amato, Francesco; Cosentino, Carlo

Chemical reaction networks (CRNs) provide an effective tool for designing robust synthetic biological feedback control circuits. Recently, we identified a two-state motif implementing ultrasensitive feedback regulation functions that allow maintaining a homeostatic equilibrium, intrinsically

embedded by the ultrasensitive characteristics itself, which is robust to environmental changes. Here, we devise a CRN that realizes the proposed two-state motif by exploiting cooperative reactions and show how increasing the level of cooperation yields adaptive, homeostatic equilibrium, robust to system uncertainties and possible disturbances.

TuCT1.17 (P2.17)

Navigating Biological Systems with Pbpk, Text Mining and Ai: In Silico Nams for the Development of Reliable and Robust Qaops, pp. 152-152

Karakoltzidis, Achilleas; Renieri, Elisavet; Papaioannou, Nafsika; Frydas, Ilias; Papageorgiou, Thanasis; Schultz, Dayna; Gabriel, Catherine; Georgiou, Nancy; Karakitsios, Spyros; Sarigiannis, Dimosthenis

In this research, we present a computational approach that commences with environmental exposure and culminates in quantitatively linking it to disease through the construction of qAOPs. Our methodology integrates various tools and techniques spanning NLP, AI, PBTK models, and in silico systems biology. HBM data is utilized to calibrate the PBTK model and translate external exposure into internal exposure. Furthermore, both in vitro and in vivo experiments are conducted to generate omics data, enabling joint pathway analysis to identify predominantly perturbed biological pathways. We introduce a text-mining toolbox to convert metabolic pathways into mechanistic systems biology models, resulting in a heterogeneous model comprising over 1300 differential equations. Model parameterization is carried out using data from the BRENDA and SABIORK databases, supplemented by AI models to estimate relevant enzyme properties, with data from HMDB utilized for model initialization. Additionally, we devise a methodology employing ML and Generative Adversarial Networks to support model initialization, generating an ML model for each endogenous metabolite, regardless of whether its concentration is known, for validation purposes. The model undergoes two executions, integrating fold change results from omics in the second run, thereby identifying metabolites with significant concentration changes and prompting the collection of publicly available data to scrutinize concentration variations and identify potential biomarkers in individuals affected by a disease. The resulting mathematical equation describing the endogenous metabolite provides a comprehensive network of interactions involving metabolites and genes. For AOP development, a bottom-up approach is employed, leveraging our knowledge of the AO and available information about the MIE, with transcriptomics, network analysis, and literature review utilized to determine the precise MIE and establish the AOP using NLP tools.

TuCT1.18 (P2.18)

Closed-Loop Modulation of Active Sensing Reveal the Critical Role of Sensory Feedback, pp. 153-154

Dipi, Furkan Sabri; Muratoğlu, Mehmet; AYDIN, Emin Yusuf; Uyanik, Ismail

This paper explores the process of active sensing, specifically in the Eigenmannia virescens, a weakly electric fish species known for implementing active sensing movements while tracking the trajectories of their refuge. A unique closed-loop experimental system was developed, enabling us to modulate these active sensing movements. This system uses an online notch filter implementation to segregate tracking and active sensing movements. By either amplifying or attenuating the active sensing movements and feeding them back to the fish's sensorimotor control process, we can manipulate and observe the effects on the fish's behavioral responses. Our findings, based on observations with N=3 fish, demonstrated that a higher level of consistency in tracking behavior was achieved when the active sensing movements were amplified.

TuCT1.19 (P2.19)

Moment Closure for a Birth-Death Model of Antimicrobial Heteroresistance, pp. 155-160

Martínez-López, Nerea; Vilas, Carlos; Pedreira, Adrián; García, Míriam R.

Developing predictive Antimicrobial Resistance (AMR) models supporting optimal treatment design to combat ”superbugs” poses a significant challenge for mathematical biology. Birth-Death (BD) processes constitute an intuitive and flexible approach for modelling biological systems' stochastic dynamics that is regaining attention due to the advances in computational techniques. This work presents a multivariate BD model of antimicrobial heteroresistance, a phenotype in which a bacterial isolate contains many subpopulations with heterogeneous antimicrobial responses. The model includes Lotka-Volterra competition between subpopulations, leading to an infinite coupled system of equations for the moment dynamics of the BD process. Then, a moment closure is proposed by assuming a log-normal distribution for a univariate BD process approximating the total population behaviour. The results are compared with stochastic simulations of the multivariate BD process during a typical time-kill assay.

TuCT1.20 (P2.20)

Metabolic Profiling of CAR-T Cell Production Process, pp. 161-161

Paxinou, Alexandra; Navarro, Sergio; Zagana, Paraskevi; Tsigalou, Aikaterini; Boutikos, Panagiotis; Juan, Manel; Klapa, Maria

In recent years, adoptive cell therapies (ACT), including Chimeric Antigen Receptor T (CAR-T) (Mohanty et al., 2019) and T-cell receptor (TCR) therapy (Tsimberidou et al., 2021) have revolutionized treatment approaches in cancer immunotherapy. CAR-T cell therapy, approved in 2017 involves the genetic engineering of immune cells (T lymphocytes) to express a synthetic Chimeric Antigen Receptor (CAR), redirecting them to seek and destroy cancerous cells. This therapy has proven to be a successful clinical treatment for hematological malignancies, including leukemia, lymphoma and multiple myeloma (Sadelain et al., 2017). However, CAR-T cell therapy is presently very expensive, and associated with risks, including life-threatening toxicities, antigen loss, T cell exhaustion in solid tumors and low durable response rates (Saborido et al., 2022)]. Moreover, centralized manufacturing, non-customizable production and clinical utilization strategies limit patient access and affect outcomes. Characterizing all steps of CAR-T cell production in respect to the patient, automating the CAR-T cell production process workflow and developing sensitive monitoring tools for early diagnosis of deviations that could be potentially addressed in situ are very important objectives for the advancement and standardization of this therapy. In the H2020 AIDPATH ("Artificial Intelligence-driven, Decentralized Production for Advanced Therapies in the Hospital") project #101016909, our group aims at the use of metabolic profiling to characterize different CAR-T cell production setups and provide high-throughput data complimenting the current bioprocess measurement set. Metabolomics has not been extensively used in CAR-T cell bioprocess development and analysis, so the project is contributing novel omic data to further our understanding of the process. In this presentation, we will show and discuss results from (a) the endo-metabolomic analysis of samples obtained from the CliniMACS Prodigy system in a clinical trial carried out at the Fundacio de Recerca Clinic Barcelona (FRCB) partner and (b) the exo-metabolomic analysis of samples from G-Rex system in different media, obtained in collaboration with UCL and CellGenix partners. Results from both analyses indicated that metabolic profiling could identify differences in the cellular physiology between different media and duration of cell cultures, which underlines the significance of metabolomics as a sensitive monitoring tool that could be used both for the CAR-T cell production process characterization and standardization. We plan to validate these results in a larger number of patients and new optimized media

TuCT1.21 (P2.21)

Developing a Standardized Meta-Database of Human Metabolic Stoichiometric Models, pp. 162-162

Pantziri, Marilena D.A.; Klapa, Maria

Genome-scale metabolic network models are essential in systems biology for studying metabolic activity dynamics and multi-omic analyses. Human genome-scale metabolic network modeling, in particular, is crucial for advancing biomedical research and drug discovery. Improvements in human genome annotation and omic technologies have led to various updated human metabolic network instances. These models are available from different repositories and in multiple formats, with varying identifiers and schemas, hardening the direct comparability, interoperability, and seamless updates alongside genome annotations. Standardizing stoichiometric models enables the educated selection of models that best fit specific research goals, facilitates direct comparison of results from various metabolomic and fluxomic studies, and highlights model components needing updates based on current human genome annotation (Pantziri and Klapa, 2022 Front Syst Biol 2:899980). Additionally, standardized human metabolic models aligned with the human genome are valuable for integrated omic investigations, enabling the direct and consistent integration of metabolic profiles and networks with gene regulation and protein interaction networks. In this context, we have been developing a standardized meta-database of human metabolic stoichiometric models enabling their comparison based on the currently assembled human metabolic reaction dataset. Our metabolic meta-database integrates information for enzyme function, reactions, metabolites, proteins, and genes, from IntEnz (www.ebi.ac.uk/intenz/), Rhea (www.rhea-db.org/), KEGG (www.genome.jp/kegg/), ChEBI (www.ebi.ac.uk/chebi/), UniProt/SwissProt (www.uniprot.org/) and GenBank (www.ncbi.nlm.nih.gov/genbank/) / Ensembl (www.ensembl.org/) databases, respectively. Through the enzymes, it is connected to the human gene ontology network, consistently linking proteins to nucleotides to genes, as implemented in our in-house standardized human protein-protein interaction (PPI) meta-database PICKLE (www.pickle.gr), forming a framework for integrated metabolomic, proteomic and transcriptomic analyses. In this study, we present the methodology of analyzing a human stoichiometric metabolic model based on the collected human metabolic reaction dataset in our meta-database. The popular human metabolic network model Recon3D (bigg.ucsd.edu/models/Recon3D) is used as a case study to illustrate our approach. NSRF2014-2020 National Infrastructure projects have funded this work: ELIXIR-GR (MIS 5002780) within the Pilot Study: Computational Metabolomics and Protein Interactomics, EATRIS-GR (MIS 5028091), the ELIXIR “Standardizing the fluxomic workflows” Implementation Study, and the ERC H2020 project JointPromise (#874837).

TuCT1.22 (P2.22)

Could Omics Shed Light to Diagnostic Concerns for HIV and Hepatitis B and C? Discussing the Issue in the Context of Blood Donor and Patient Data from a Major Greek Hospital, pp. 163-164

Matsagos, Spyridon (Spyros); Anastasiou, Eleni; Kafkarisiou, Stamatina; Giannopoulou, Vassiliki; Kougia, Sophia; Alepi, Chrysoula

Hepatitis B (HBV) and C (HCV) and HIV infections remain a significant global health issue. However, in diagnostic testing, some cases have values near the detection limit of the methods used, necessitating repeat and confirmatory tests. These may not always yield conclusive results, in addition to the challenge of an accurate diagnosis. The aim of this study is to determine the prevalence of HBV, HCV, and HIV among patients and blood donors who visited the General Hospital "Tzaneio", one of the main state hospitals in the metropolitan area of the Greek capital, between January 1, 2016, and December 31, 2023. Furthermore, this study was conducted to identify cases with borderline values that require repetition or confirmation methods. This underscores the importance of incorporating a comprehensive omics approach that can provide a more holistic understanding of these infections. Positive results for HBV, HCV, and HIV were selected according to the manufacturer's cut-off. Depending on the detection value, they were divided into positive and borderline positive results and were further analyzed to determine the prevalence of the diseases between the hospital blood donors and patients across this eight-year period. The prevalence of HBV, HCV, and HIV in the general population was observed higher than that in blood donors. Although the screening and confirmatory diagnostic methods are at a high level, a percentage of subjects tested cannot obtain a clear result, probably due to cross-reactions or other factors. The integration of holistic multi-omic analyses is expected to contribute significantly to diagnosis, prognosis and individualized therapeutic approaches, enabling the hospital labs to derive clear conclusions for more cases.

TuCT1.23 (P2.23)

Dynamic Feedback Control in Plant Circadian Rhythms, pp. 165-165

Aleiferis, Spyridon; Klapa, Maria

Similar to animals, plants have circadian rhythms that are synchronized with the daily cycle of light and dark in order to maximize their growth, development, and metabolism. Understanding the underlying mechanisms of this circadian regulation has potential implications for agricultural productivity (Belbin et al., 2019). In this work, we provide a comprehensive overview of how the mechanisms of dynamic feedback in plant circadian rhythms, and how they regulate the temporal evolution of plant physiology (Hurley et al., 2016) have been analysed by cybernetic principles. Cybernetic models aim at explaining how systems demonstrate stability and adaptation through feedback mechanisms. At the core of these systems, molecular feedback loops involving clock genes, regulate the expression of downstream target genes and influence physiological processes (Noordally et al., 2013). By integrating control theory insights, we examine how these feedback loops enable plants to anticipate environmental changes, synchronize with the day-night cycle, and coordinate metabolic activities. Especially in plants, for which the circadian clocks are more decentralized, compared to mammals (Endo, 2016), concepts from complex system control theory (Liu and Barabási, 2016) can be applied incorporating different models of circadian clocks (Chakravarty et al., 2023; Pokhilko et al., 2012). This approach yields insights that improve our knowledge of plant circadian regulation and present prospects for agricultural practices, including timing crop development and stress resilience. Furthermore, this work emphasizes the relevance of feedback loops for examining biological timekeeping systems in a larger context and how cybernetic modelling could be applied in the context of user-friendly platforms to monitor their consequences in the context of the objectives of ecological resilience and sustainable agriculture.

TuCT1.24 (P2.24)

A Systems Theoretical Formalism to Characterize the Attractor Landscape of Solid Tumors for Designing Immuno-Therapeutic Strategies, pp. 166-166

Bhattacharya, Priyan; Vadigepalli, Rajanikanth

Non-responsive therapy outcomes have been a persistent problem in cancer treatment. Predicting the likelihood of non-responsiveness based on the pre-treatment composition of the tumor microenvironment (TME) can aid the design of combination treatment strategies toward an improved prognosis. We developed a systems-theoretic formalism to unfold the mechanisms driving solid tumor growth, non-responsiveness to Immune Checkpoint Inhibition (ICI), and recurrence. The proposed formalism begins with reconstructing the TME network containing different tumor epithelial, stromal, and immune cell types, each in multiple functional states and relevant molecular agents mediating cellular signaling and cell-cell interactions. We performed a systems-theoretic analysis to delineate the attractor landscape of the TME system in response to a range of perturbations induced by molecular interventions. We identified five sets of attractors corresponding to Immune deficient, Fibro-desert, Immune and Fibro-deficient, Immune-

rich and Fibro-rich TME subtypes. A graph theory-enabled structural analysis of the TME network revealed that non-responsivity to ICI arises due to i) absence or ii) vanishing reachability from the node representing anti-PD1/PDL1 drug to the tumor cells. While the former can be attributed to the attractor sets reflecting immune desert phenotype, the latter is an emergent property around the fibro-rich-like attractors. Based on the analysis, we propose that ICI alters the underlying dynamical system's attractor geometry (location of stable, steady states). Our results hold for a large class of smooth biochemical kinetics with monotone interactions and (semi-)concave proliferation rules typically employed in modeling biological systems. Finally, we designed novel TME subtype-specific combinatorial perturbations that can restore the reachability of the ICI drugs to the tumor cell states. These intervention strategies can be implemented by modulating inflammatory components specific to TME subtypes, leading to efficacious ICI therapy. Overall, we propose a generalized formalism that can capture the salient TME properties and aid in designing appropriate intervention strategies to improve the solid tumor prognosis.

13:15-15:00 ROOMS CALYPSO CALYPSO + Veranda PERGOLA

Poster Session II - Presentations (CALYPSO) + Lunch Buffet (Veranda PERGOLA)

Chair: Boada, Yadira — Techical University of Valencia

TuET1 Room NAFSIKA

Session 4: Control in Biology (Regular Session)

Chair: Picó, Jesús — Universitat Politecnica De Valencia

15:00-15:20 TuET1.1 (OP13)

Multicellular PID Control of Gene Expression in Microbial Consortia, pp. 167-167

Martinelli, Vittoria; Salzano, Davide; Fiore, Davide; di Bernardo, Mario

Synthetic Biology aims at embedding cells with new functionalities using engineering principles, with applications ranging from health treatments to bioremediation. However, due to the intrinsically nonlinear and stochastic nature of biochemical processes, it is necessary to develop strategies to enhance the reliability and robustness of the synthetically engineered circuits. This can be done by engineering theory-driven gene regulatory networks aimed at regulating the phenotype expressed by the cells. However, the realization of such controllers is limited by availability of suitable biological components. Thus, controllers with a simple structure, such as the PID controllers, are particularly appealing in this context, as they guarantee precise and robust regulation without the requirement of implementing complex mathematical operations. Several implementations of biomolecular PID controllers have been proposed in the past years. However, most of these solutions require embedding the control logic within the same cell hosting the process. This could cause excessive metabolic burden, as well as a lack of modularity, limiting the applicability of the developed controllers. To overcome these problems, we propose a multicellular implementation of a biomolecular PID controller, in which the proportional, integral and derivative actions are each implemented in a different population within a microbial consortium. These populations are interfaced using quorum sensing molecules with a target population hosting the process that needs to be controlled. We derive analytical conditions to guide the design of a consortium with specific transient and static performance using the root contours method and we numerically validate the the performance and robustness of the proposed multicellular control strategy via extensive in silico experiments in BSim, a realistic agent-based simulator of bacterial populations.

15:20-15:40 TuET1.2 (OP14)

Optimizing Fed-Batch Processes with Dynamic Control Flux Balance Analysis, pp. 168-173

Gotsmy, Mathias; Giannari, Dafni; Mahadevan, Radhakrishnan; Zanghellini, Juergen

Fed-batch processes are prevalent in biotechnological industries, but design of experiments often results in sub-optimal conditions due to incomplete solution space characterization. We employ a single-level dynamic control (DC) algorithm for dynamic flux balance analysis (dFBA), enhancing efficiency by reducing Karush-Kuhn-Tucker (KKT) condition constraints and adapting the algorithm for predicting optimal process length. In a growth-decoupled plasmid DNA production case study, we predict the optimal feeding profile and switching time between growth and production phase. Comparing our algorithm to its predecessor shows a speed-up of at least a factor of four. When the process length is part of the objective function the speed-up becomes considerably larger.

15:40-16:00 TuET1.3 (OP15)

Linking Intra and Extra-Cellular Metabolic Domains Via Neural-Network Surrogates for Dynamic Metabolic Control, pp. 174-179

Espinel-Ríos, Sebastián; L. Avalos, Jose

We outline a modeling and optimization strategy for investigating dynamic metabolic engineering interventions. Our framework is particularly useful at the early stages of research and development, often constrained by limited knowledge and experimental data. Elucidating a priori optimal trajectories of manipulatable intracellular fluxes can guide the design of suitable control schemes, e.g., cyber(ge)netic or in-cell approaches, and the selection of appropriate actuators, e.g., at the transcriptional or post-translational levels. Model-based dynamic optimization is proposed to predict optimal trajectories of target manipulatable intracellular fluxes. A challenge emerges as existing models are often oversimplified, lacking insights into metabolism, or excessively complex, making them difficult to build and implement. Here, we use surrogates derived from steady-state solutions of constraint-based metabolic models to link manipulatable intracellular fluxes to the process exchange rates of structurally simple hybrid dynamic models. The latter can be conveniently used in optimal control problems of metabolism. As a proof of concept, we apply our method to a reduced metabolic network of Escherichia coli considering two different scenarios of dynamic metabolic engineering.

16:00-16:20 TuET1.4 (OP16)

Robust Model Predictive Control of a Vaccine Production Unit, pp. 180-185

Benavides, Micaela; Dewasme, Laurent; Gerkens, Pascal; de Lannoy, Gaël; Vande Wouwer, Alain

In this paper, nonlinear model predictive controllers (NMPC) are proposed to optimize the biomass productivity of yeast fed-batch cultures. Their predictions are driven by a mechanistic model developed using a few industrial vaccine production data sets. The limited amount of data causes high parametric uncertainty levels and, to address this issue, a robust tube-based MPC is proposed and its robustness is assessed by a Monte-Carlo analysis, and compared to the classical MPC formulation.

16:20-17:00 Room NAFSIKA

Coffee Break

TuFT1 Room NAFSIKA

Session 4 (cont'd): Control in Biology (Regular Session)

Chair: Picó, Jesús — Universitat Politecnica De Valencia

17:00-17:30 TuFT1.1 (Invited Lecture 6)

T-Cell Engagers: Some Lessons Learned from a Minimal Mechanistic Model of Trimer Formation, pp. 186-186

Lai, Massimo; Pichardo-Almarza, Cesar; Verma, Meghna; Kimko, Holly

T-cell engagers (TCEs) are a promising therapeutic strategy for

solid tumours and haematological malignancies. They are a class of bispecific antibodies designed to act as a cross bridge between T-cells and target malignant cells, by engaging T-cell receptors (TCRs) on one arm and tumor-associated antigens (TAAs) on malignant cells with the other arm. It is agreed upon that TCE efficacy is related to the ability of the compound to stimulate T-cell effector function, which depends on the formation of trimers (often referred to as “trimeric synapses” or “ternary complexes”).

It is known that TCEs follow a bell-shaped relationship between antibody concentration and trimer concentration. If we assume that trimer formation is the main efficacy biomarker driving T-cell effector function, there is a point of diminishing returns beyond which efficacy is expected to plateau or even decrease at higher doses. Theoretical models can capture this dynamic which is further observed in vitro. This “hook effect” phenomenon can potentially arise for any bispecific molecule. The mechanistic rationale for it is that trimer formation can only occur if both an antibody-receptor dimer and an unoccupied receptor are simultaneously available. Excess TCE saturates all available tumor receptors or effector receptors, thus biasing the equilibrium towards dimers instead of trimers. We present an exploratory analysis for a generic bispecific TCE, targeting CD3 on T-cells and a tumor-specific receptor on cancer cells, and discuss implications for compound design and clinical dosing. We utilised a minimalistic kinetic model of trimer formation, with the simplifying assumption that reactions occur in a well-mixed compartment. We used the model to investigate the interplay between drug exposure, target affinity, and target expression levels.

Target expression levels, which cannot be controlled, may differ among patients. We found that the exposure at which the efficacy plateau is predicted depends mainly on the relative affinities of the antibody for each target, but not on target expression levels. Therefore, the optimal exposure level may not be “patient-specific”, but rather “compound-specific”.

17:30-18:00 TuFT1.2 (Invited Lecture 7)

It's All about Time! the Critical Role of Circadian Rhythms in Regulating Health, Disease, and Pharmacology, pp. 187-187

Androulakis, Ioannis

Light and temperature constitute two major entrainers of the circadian timing system. Understanding how photic signals are transduced through the SCN and how core body temperature influences peripheral cells is critical for understanding the emergence of biological rhythms in the peripheral tissues. This work discusses mechanistic mathematical models that capture the essential hierarchical structure of the photic and temperature signal transduction through the SCN leading to rhythmic patterns of endocrine hormones (cortisol) and peripheral clock genes activation with profound downstream physiological and pharmacological effects. We analyze the implications of disrupted light signals in the form of (social) jetlag and shift work and the implications of alterations in core body temperature rhythms. Such model predictions would add insights toward understanding the organization of the central timing system and the health implications of disrupting and restoring circadian rhythms. Finally, we discuss how population studies examining human behavior can shed light on the role the disruption of circadian rhythms plays in the development of chronic disease.

TuGT1 Room NAFSIKA

Keynote Lecture 2 (Keynote Session)

Chair: Hancock, John University of Ljubljana

18:00-19:00 TuGT1.1

*Two Decades of BioModels: Promoting FAIReR Sharing and Reproducibility of Computational Models in the Life Sciences**

Malik-Sherif, Rahuman

BioModels is a world-leading repository of computational models in the life sciences. Over the past two decades, BioModels has evolved from primarily curating ODE-based kinetic models to curating models across diverse modelling approaches. Originally established in 2005, BioModels now serves as a key repository for a wide range of computational models, ensuring they are Findable, Accessible, Interoperable, Reusable, and, more importantly, Reproducible (FAIReR). To investigate the reproducibility crisis in systems biology modelling, BioModels systematically attempted to reproduce 455 kinetic models published in peer-reviewed research articles. The study revealed that nearly half (49%) of these models could not be reproduced using the information provided in the manuscripts. This analysis exposed a widespread problem in the peer-review process, leading BioModels to propose an 8-point reproducibility scorecard to help authors, reviewers, and editors address this crisis. BioModels has developed several specific initiatives to address reproducibility challenges across different model types: (i) In constraint-based models, such as genome-scale metabolic models (GEMs), flux values reported in manuscripts are often not unique, making it difficult to numerically reproduce these models. To address this, BioModels developed the FROG analysis, which standardizes model evaluation and improves reproducibility by facilitating the public sharing of reference datasets. (ii) Stochastic models generate different numerical outcomes with each run, complicating the assessment of their reproducibility. The EFECT method was created to evaluate the reproducibility of stochastic simulation results by assessing whether the distributional differences in outcomes are consistent and reproducible. (iii) Machine learning (ML) models, along with their datasets and associated tools, are often scattered across various platforms and sometimes incomplete, complicating the process of assembling them and reproducing results. The BioModels-ML project was launched to standardize and streamline the sharing of ML models, ensuring they are FAIR and reproducible.

19:30-23:00

Guided Tour of the Old Town of Corfu (Unesco Monument) + Gala Dinner in Corfu town

Program and Abstracts Wednesday September 11

09:00-10:30 WeAT1 Room NAFSIKA **General Session 5** – **Systems biology for Health** *Session Chair: Yannis Androulakis, Rutgers University, USA*
10:30-11:00 Coffee Break
11:00-11:30 WeBT1 Room NAFSIKA **General Session 5** – **Systems biology for Health** *Session Chair: Yannis Androulakis, Rutgers University, USA*
11:30-12:30 WeCT1 Room NAFSIKA **Award Ceremony & Closing Remarks** *Chairs: Maria I. Klapa, FORTH/ICE-HT, Greece; Kristel Bernaerts, KU Leuven, Belgium; Alejandro Vignoni, Technical University of Valencia, Spain*

Technical Program for Wednesday September 11, 2024

WeAT1 Room NAFSIKA

Session 5: Systems Biology for Health (Regular Session)

Chair: Androulakis, Ioannis — Rutgers University

09:00-09:30 — WeAT1.1 (Invited Lecture 8)

*Computational Identification of Cancer Immunotherapy Targets**

Szomolay, Barbara

The interaction between T-cell receptors (TCRs) and peptides is highly degenerate: a single TCR may recognize about one million different peptides in the context of a single MHCI molecule. On the other hand, TCR recognition is fundamentally peptide- and/or MHC-specific: the functional sensitivity, which can be viewed as experimental realisation of the TCR triggering rate, is large enough only for minute fraction of all possible ligands. TCR triggering rate and degeneracy are mathematical concepts that are fundamental for an approach that uses length-matched combinatorial peptide library (CPL) scan data to search protein databases and to rank peptides in order of likelihood of recognition. This CPL-based database screening can, to a large extent, accurately identify self-peptides that triggered the CD8 T-cell. I will present different applications of the CPL-based approach that contributed to our understanding of cancer immunity by identifying potential targets for tumor-specific T-cells.

09:30-09:50 — WeAT1.2 (OP17)

Modelling Rate of Exogenous Glucose Appearance for Biomedical Applications Using Condition Generative Models, pp. 188-193

Noguer, Josep; Contreras, Ivan; Beneyto, Aleix; Vehi, Josep

The assessment of oral carbohydrate intake and its rate of exogenous glucose appearance is crucial for monitoring blood glucose in patients who suffer from diabetes and also for healthy individuals, as it is one of the major factors involved in human metabolism. Its accurate modelling is necessary when developing methodologies to mimic the physiological processes within the human body. Considering the recent advancements in data-driven methods that demand non-deterministic solutions to simulate real-life scenarios, this study proposes a novel approach based on conditional generative adversarial models to introduce realistic variability to the models in the state of the art, which are incapable of representing the full variety of scenarios due to their deterministic nature.

09:50-10:10 — WeAT1.3 (OP18)

Investigating Differences in the GWAS-Based Protein-Protein Interaction Network of Blood Pressure Regulation Due to Ancestry or Transcript Consequence Severity, pp. 194-199

Tsare, Evridiki-Pandora; Klapa, Maria; Moschonas, Nikos

Genome-wide association studies (GWAS) have been valuable for the identification of genetic factors associated with complex diseases or traits. GWAS findings can be enhanced if analysed in the context of protein-protein interaction (PPI) networks, as the related pathophysiology results from dysfunction of interacting polyprotein pathways. In a recent study, we reconstructed the PPI network of blood pressure regulation (BP) based on a systematically-curated GWAS meta-database and network extension principles. Our meta-database enables the selection of GWAS-data of different ancestries and/or different Ensembl-defined transcript consequence severities. Thus, this study aimed at investigating any differences in the BP PPI network, due to (a) ancestry, by comparing the most-abundant European and Asian ancestry GWAS datasets, and (b) variant consequence severity, by excluding single nucleotide polymorphisms (SNPs) involved only in “modifier” categories, of difficult to predict impact. We identified that 82% of the collected BP-SNPs are from European-specific studies, with only 11% from Asian-specific, validating the need to augment the GWAS-data from other than European ancestries. Thus, only 7% vs 83% of the 1170 BP GWAS-proteins originate from Asian- and European-specific studies, respectively, with 2% (24) identified as Asian-specific vs ~45% (524) as European-specific GWAS-proteins. In the second part of the study, we found that the vast majority (85%) of the BP-SNPs with protein-coding transcript consequences are only intron variants (‘modifier' category). Hence, the PPI network based on the SNPs in other than “modifier” categories included 142 proteins, with 12 in the largest connected component. However, while the relevant interactome is much smaller than the full, when extended based on our shortest-path approach, it revealed the same BP-significant pathways. This result supports the need to upgrade the information content of GWAS-data through network analysis.

10:10-10:30 — WeAT1.4 (OP19)

*Multi-Omics Analysis Unveils the Impact of DEHP on Metabolic Disorders: Insights from OBERON's in Vivo and in Vitro Results**

Papageorgiou, Thanasis; Papaioannou, Nafsika; Frydas, Ilias; Gabriel, Catherine; Schultz, Dayna; Boronat-Belda, Talía; Ferrero, Hilda; Al-Abdulla, Ruba; Touma, Charbel; Le Mentec, Hélène; Lagadic-Gossmann, Dominique; Karakitsios, Spyros; Podechard, Normand; Alonso-Magdalena, Paloma; Langouet, Sophie; Audouze, Karine; Anesti, Ourania; Sarigiannis, Dimosthenis

Numerous endocrine-disrupting chemicals (EDCs), such as phthalates, are widely used in everyday products, resulting in their release into the environment. Di-2-ethylhexyl phthalate (DEHP), one of the chemicals within the phthalates, poses significant health

risks to the development of metabolic disorders such as obesity, diabetes, insulin resistance, and non-alcoholic fatty liver disease (NAFLD). Within the OBERON project we employed a multi-omics pathway analysis, utilizing both in vitro (EndoC-βH1 and HepaRG cell lines) and in vivo (zebrafish at 5 days post-fertilization) models exposed to DEHP, to provide an integrative interpretation of omics data beyond individual biomarkers. This multi-omics approach aims to uncover mechanisms behind biomarker dysregulation leading to metabolic disorders. For transcriptomics, Agilent microarrays were used to determine the differentially expressed genes (DEGs) between control and treatment groups, and DEGs were identified using the limma R package. Untargeted metabolomics analysis was performed using an Agilent 6540 QTOF using two different analytical columns (RP and HILIC) in both positive and negative ionization modes. Data pre-processing, and identification of differentially expressed metabolites (DEMs), as well as the multi-omics data integration were performed with R-based packages including xcms, MetaboAnalystR, and mixOmics. This comprehensive analysis identified disrupted pathways linked to steroid hormone biosynthesis (HepaRG: 4 metabolites - EndoC-βH1: 1 DEG and 2 metabolites - Zebrafish: 1 DEG and 3 metabolites) and the FoxO Liver (HepaRG: 19 DEGs - EndoC-βH1: 2 DEGs Zebrafish: 3 DEGs) and MAPK signaling pathways (HepaRG: 19 DEGs and 1 metabolite - EndoC-βH1: 4 DEGs – Zebrafish: 5 DEGs), indicating potential biomarkers and pathways involved in DEHP's toxicity mechanisms in both in vitro and in vivo models. In conclusion, our multi omics study offers insights into the underlying mechanisms of metabolic disorders and identifying potential biomarkers for assessing DEHP's health risks.

10:30-11:00 Room NAFSIKA

Coffee Break

WeBT1 Room NAFSIKA

Session 5 (cont'd): Systems Biology for Health (Regular Session)

Chair: Androulakis, Ioannis — Rutgers University

11:00-11:30 WeBT1.1 (Invited Lecture 9)

Living Cures: Building a Programmable Therapeutic Platform for Optimization and Delivery of Immunostimulatory Proteins, pp. 200-200

Biarnes Carrera, Prokarium; Petsiou, Georgia; Oke, Oluwatobiloba; Storch, Marko; Glanville, Nicholas; Deban, Livija

Despite significant advancements over the past decades, cancer treatment remains a challenge. Immunotherapy emerged as promising therapeutic avenue aimed at employing targeted strategies to train the patients' immune system for recognition and elimination of cancer cells. Whilst immunotherapy fundamentally changed how we treat cancer, many cutting-edge treatments still grapple with limited efficacy and severe side effects stemming from obstacles in drug delivery, such as insufficient tumor penetration, rapid drug clearance, or off-target effects in healthy tissues. Prokarium is developing an innovative immunotherapy Living Cures platform aimed at overcoming these challenges by harnessing the potential of tumor-colonizing bacteria to deliver immunomodulatory molecules, such as cytokines and chemokines, for treatment of solid tumors. Expression of complex therapeutic molecules in bacterial hosts often leads to inactive inclusion bodies and minimal active protein production. Prokarium's Directed Evolution pipeline addresses this challenge by optimizing cytokine expression and secretion in bacteria while preserving functionality. Here, we present the results of applying the pipeline to three cytokines: IL-15, IL-18, and IL-21. Cytokines were fused with a curated library of signal peptides to guide protein localization to the periplasm, followed by directed evolution screening that identified stability-enhancing mutations. Soluble candidates were evaluated in appropriate cell-based assays and lead designs were purified for final validation. IL-18 underwent additional rounds of engineering to create a novel decoy-resistant variant. These advancements resulted in therapeutic candidates integrated into a proprietary Salmonella strain capable of accepting multiple circuits simultaneously, providing a flexible plug-and-play cancer immunotherapy platform, and paving the way for preclinical testing.

WeCT1 Room NAFSIKA

Closing Session

11:30-12:30

Award Ceremony & Closing Remarks

Chair: Klapa, Maria I. — NOC Chair, Institute of Chemical Engineering Sciences, Foundation for Researc & Technology, Hellas (FORTH/ICE-HT), Greece

Co-chair: Vignoni, Alejandro — Universitat Politècnica De Valencia

Author Index

C: Chair
CC: Co-Chair
M: Moderator
PA: Panelist
*: No pdf file attached

Keyword Index

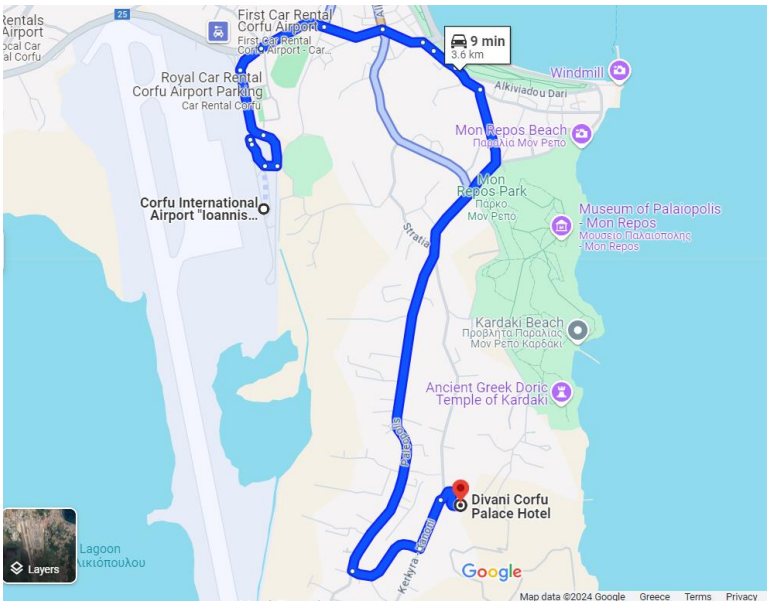
FOSBE 2024 Keyword Index

Maps

Divani Corfu Palace Hotel, Corfu Ionian Island

Nafsikas 20, Corfu Island, Greece

https://divanicorfuhotel.com/el/



Route in google maps from the Airport to Divani Corfu Hotel Palace

(39.59910618217531, 19.922358559385163)