Abstract Book

3rd International SystemsX.ch Conference on Systems Biology

September 4–7, 2017
ETH Zurich, Switzerland

SystemsX.ch
The Swiss Initiative in Systems Biology

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Contents

Dear colleagues,

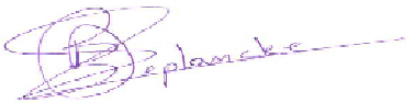
It is our great pleasure to welcome you to the 3rd International SystemsX.ch Conference on Systems Biology 2017 in Zurich.

As this is the final event of the SystemsX.ch Initiative, which will officially end in 2018, it's appropriate to briefly look back and consider its achievements. SystemsX.ch was launched with the ambitious goal of generating know-how, the technical, intellectual, and financial resources as well facilities to transform Switzerland into one of the leading systems biology research centers in the world. Since its official start in 2008, 248 projects have been approved involving a remarkable 401 distinct research groups and more than 2,100 researchers. It is therefore fair to say that SystemsX.ch has been a major driver in transforming not only Swiss biology research, but also worldwide research (through its many collaborations), from a more descriptive, qualitative discipline into a quantitative, predictive science. Emphasis has been placed on bridging disciplines, bringing together experts in engineering and computational sciences with biologists and clinicians to address a diverse array of outstanding biomedical questions in an innovative and holistic fashion. To broadcast these achievements and make them accessible to the public, SystemsX.ch has produced an insightful documentary. We invite you all to have a look when it becomes available on the SystemsX.ch website, and learn about the history of SystemsX.ch and specifically about several of its research projects which collectively exemplify the ambitious scope of this groundbreaking initiative.

In the meantime, please sit back and enjoy our program, featuring two keynote lectures, talks from leading international researchers as well as presentations from our own SystemsX.ch project leaders over the course of four days. In addition to the program of invited speakers, each session will feature short talks selected from the abstract submissions, and there will be poster sessions, providing young scientists a platform for discussing their work. The conference is divided into the five sessions Synthetic Biology, Physics of Living Systems, Single-Cell Biology, Systems Genomics, and Medical Systems Biology.

We hope that this conference will encourage lively scientific exchange between participants, and serve as another important motivator to sustain the spirit of SystemsX.ch by keeping quantitative, predictive science alive and well.

Thank you for your participation.



Bart Deplancke
Chair of Scientific Committee

Monday, September 4, 2017

14:20 Excursion to the Masoala Rainforest at Zoo Zurich

17:00 **Keynote lecture: Trigger waves in cell signaling**
James Ferrell, *Stanford University, USA*

18:30 **SystemsX.ch Film Launch Party**
Dozentenfoyer, ETH Zurich Main Building

Tuesday, September 5, 2017 morning

Synthetic Biology

Chair: Yolanda Schaerli, *University of Lausanne*

09:45 **Directing *in vitro* organogenesis through engineered microenvironments**
Matthias P. Lutolf, *Institute of Bioengineering, EPFL, Switzerland*

10:15 **A synthetic framework on membrane protein organisation modulated by feedback reactions**
Chieh Hsu, *University of Kent, UK*

10:30 **Synthetic biology unveils control principles of stochastic gene choice and mRNA turnover**
Attila Becskei**,** *University of Basel, Switzerland*

11:00 Break
D-Level Foyers

11:30 **Single-cell dynamics, from bacterial growth to organoid infection**
Sander Tans, *FOM Institute AMOLF, Netherlands*

12:15 **Spatiotemporal Control of TGF-beta Signaling with Light**
Zhike Zi, *MPI for Molecular Genetics, Berlin, Germany*

12:30 Lunch
Foodmarket, D-Level

13:20 Poster session, topics 1 & 2
D-Level Foyers

Tuesday, September 5, 2017 afternoon

Physics of Living Systems

Chair: Félix Naef, *EPF Lausanne*

14:30 **Diversity of immune receptor repertoires**
Aleksandra Walczak**,** *Ecole Normale Supérieure, France*

15:15 **A living mesoscopic cellular automaton made of skin scales**
Anamarija Fofonjka, *University of Geneva, Switzerland*

15:30 **Exploring the generation and coordination of forces driving dorsal closure during Drosophila embryogenesis**
Damien Brunner, *University of Zurich, Switzerland*

16:00 Break
D-Level Foyers

16:30 **Nanopores in 2D materials**
Aleksandra Radenovic, *EPFL, Switzerland*

17:00 **Rules of thumb in gene control: optimality and suboptimality of a bacterial growth law**
Benjamin D. Towbin, *Weizmann Institute of Science, Israel*

17:15 **Upside Down and Inside Out: The biomechanics of cell sheet folding**
Ray Goldstein, *University of Cambridge, UK*

18:00 Drinks and poster session, topics 3 & 4
D-Level Foyers

Wednesday, September 6, 2017 morning

Single-Cell Biology

Chair: Lucas Pelkmans, *University of Zurich*

09:00 **The power of ONE: Immunology in the age of single-cell genomics**
Ido Amit, *Weizmann Institute of Science, Israel*

09:45 **Unraveling Cortical Development: Analyzing population and single-cell RNA-Seq data**
Zahra Karimaddini, *ETH Zurich, Switzerland*

10:00 **From single-cell perturbation to subcellular analysis using fluidic force microscopy**
Julia Vorholt, *ETH Zurich, Switzerland*

10:30 Break
D-Level Foyers

11:00 **Long-term single-cell quantification: New tools for old questions**
Timm Schroeder*, ETH Zurich, Switzerland*

11:30 **Dynamic single cell analysis of a cell fate decision system**
Serge Pelet, *University of Lausanne, Switzerland*

11:45 **Reconstructing human development using single-cell transcriptomics**
Barbara Treutlein, *MPI Leipzig, Germany*

12:30 Lunch
Foodmarket, D-Level

13:20 Poster session, topic 5
D-Level Foyers

Wednesday, September 6, 2017 afternoon

Systems Genomics

Chair: Bart Deplancke, *EPF Lausanne*

14:30 **Survey of coding variation in human transcription factors reveals prevalent DNA binding changes**
Martha Bulyk, *Harvard Medical School, USA*

15:15 **Isoform-specific localisation of DNMT3A regulates DNA methylation turnover at bivalent CpG islands**
Tuncay Baubec, *University of Zurich, Switzerland*

15:30 **Contribution of non-coding DNA to complex traits and cancer**
Emmanouil Dermitzakis, *University of Geneva Medical School, Switzerland*

16:00 Break
D-Level Foyers

16:30 **Cracking the genetic basis of human longevity**
Zoltan Kutalik, *University of Lausanne, Switzerland*

17:00 **Systems analysis reveals high genetic and antigen-driven predetermination of antibody repertoire diversity and development**
Ulrike Menzel, *ETH Zurich, Switzerland*

17:15 **Personalized medicine approaches based on gut microbiota**
Eran Segal, *Weizmann Institute of Science, Israel*

18:30 Apero and conference dinner (reservation necessary)
Steingarten, outside the Foodmarket, D-Level

Thursday, September 7, 2017 morning

Medical Systems Biology

Chair: Patrick Matthias, *Friedrich Miescher Institute*

09:00 **Deciphering Host-Virus Interactions to Cure HIV**
Karin J. Metzner, *University Hospital Zurich, Switzerland*

09:30 **Detecting localized amino acid kinetics through mass spectrometry imaging of stable isotopes**
Zita Soons, *Maastricht University, Netherlands*

09:45 **Studying the yeasts of yesterday to generate the beer yeasts of tomorrow**
Kevin Verstrepen, *KU Leuven, Belgium*

10:30 Break
D-Level Foyers

11:00 **A combined experimental and computational strategy identifies key cellular mechanisms for proliferation in pre-erythrocytic malaria parasites**
Volker Heussler, *University of Bern, Switzerland*

11:30 **Metabolic modeling of *Toxoplasma gondii*: toward a tachyzoite-specific network**
Aarti Krishnan, *University of Geneva, Switzerland*

11:45 **Use of massively parallel sequencing technologies to identify somatic mutations**
Peter Campbell, *Wellcome Trust Sanger Institute, UK*

12:30 Poster awards

12:40 **Keynote lecture: Systems Biology in Action: 1. Design of cancer combination therapy; 2. Prediction of 3D structures of biomolecular complexes**
Chris Sander, *Dana-Farber Cancer Institute and Harvard Medical School, Boston, USA*

13:40 Lunch and departure
Foodmarket, D-Level

Keynote Speakers

Keynote speaker

Trigger waves in cell signaling

James Ferrell

Stanford University, United States

Xenopus laevis eggs are huge cells, so that even a freely diffusing protein would take hours to make it from the center of the egg to the cortex. Despite this, mitosis takes place quickly and in a spatially coordinated fashion in fertilized *Xenopus* eggs. Because there is positive feedback in the circuit that regulates Cdk1, the egg has the possibility of supporting trigger waves of Cdk1 activation that spread over large distances faster than diffusion alone would allow. We carried out experiments to look for these trigger waves, using cell free *Xenopus* egg extracts in thin Teflon tubes and a fluorescence microscopy assay for mitosis. We found that Cdk1 activation does, as hypothesized, spread linearly through these extracts at a constant speed of ~1 μm/sec, allowing Cdk1 activity to spread from the center to the cortex of an egg in about 10 min. We suspect that trigger waves may be found in other signaling systems where events need to be coordinated over long distances.

Keynote speaker

Systems Biology in Action: 1. Design of cancer combination therapy; 2. Prediction of 3D structures of biomolecular complexes

Chris Sander

Dana-Farber Cancer Institute and Harvard Medical School, Boston, United States

Part 1: Cells and organisms have evolved as robust to external perturbations and adaptable to changing conditions. This capacity poses severe problems for cancer patients. Some targeted anti-cancer drugs work remarkably well, yet resistance is almost certain to emerge. Three particular scientific challenges arise: (1) discover the escape routes in response to drugs and how to block the exits by combinatorial intervention; (2) in The Cancer Genome Atlas empirically describe the landscape of oncogenic alterations for improved therapeutic navigation and (3) use experimental perturbation biology (systematic perturbation coupled with rich observation of response, such as changes in protein levels and protein modifications) to derive executable network models for cancer cells that guide the development of combination therapy. Work done in collaboration with Anil Korkut, Evan Molinelli, Martin Miller, Wei Qing Wang, Xiaohong Jing, Alex Root, Deb Bemis, David Solit, Christine Pratilas, Emek Demir, Arman Aksoy, Onur Sumer, Özgün Babur, Andrea Pagnani, Martin Weigt, Riccardo Zecchina, Giovanni Ciriello, Nikolaus Schultz, Sven Nelander, Debora Marks et al. Ref: **Perturbation biology nominates upstream–downstream drug combinations in RAF inhibitor resistant melanoma cells** http://bit.ly/2cB4jNv.

Part 2: Collaborative efforts combining computational biology, structural biology and statistical physics expertise provide a solution to the computational protein folding problem. Genomic sequences contain rich evolutionary information about functional constraints on macromolecules such as proteins. This information can be efficiently mined to detect evolutionary couplings between residues in proteins and address the long-standing challenge to compute protein and RNA three-dimensional structures from sequences alone. Substantial progress on the evolutionary couplings approach, since the initial attempts in 1994, has become possible because of the explosive growth in available sequences and the application of global statistical methods, such as maximum entropy distillation of

correlated mutation patterns. In addition to proteins and RNA 3D structure, this powerful analysis of covariation helps identify functional residues involved in ligand binding, complex formation and conformational changes. We expect computation of evolutionary covariation patterns to help elucidate the full spectrum of protein and RNA structures, their functional interactions and evolutionary dynamics. Collaboration between the Sander and Marks (Harvard Medical School) groups, as well as initially with Martin Weigt, Andrea Pagnani and Riccardo Zecchina at Politecnico di Torino. Use the http://evfold.org server to compute EVcouplings and to predict 3D structure for large sequence families. Ref: **Protein 3D Structure from high-throughput sequencing** http://bit.ly/tob48p. Ref: **3D RNA and Functional Interactions from Evolutionary Couplings** http://bit.ly/3D_RNA.

Synthetic Biology

Chair:
Yolanda Schaerli
Department of Fundamental Microbiology
University of Lausanne

Speaker

Single-cell dynamics, from bacterial growth to organoid infection

Sander Tans

FOM Institute AMOLF, Netherlands

We use time-lapse microscopy to measure the dynamics of individual cells, focusing on a number of different questions. Examples include the relation between fluctuations in the expression of metabolically active enzymes and cellular growth, how cells control their size in the presence of external and internal perturbations, and a surprising observation of motility in epithelial cells that is triggered by viral infection.

Speaker

Directing *in vitro* organogenesis through engineered microenvironments

Matthias P. Lutolf

Institute of Bioengineering and Institute of Chemical Sciences and Engineering, EPF Lausanne, Switzerland

The earliest steps of development are characterized by cellular reorganization and differentiation within a 3D microenvironment. This 3D context allows for a complex interplay between biochemical and mechanical signals, and governs important cellular rearrangements leading to morphogenesis. In vitro approaches have attempted to recapitulate key features of these processes, and it has become possible to generate an increasing variety of self-organizing tissue constructs termed ‘organoids’. While important aspects of the 3D in vivo organization have been recreated using organoids, such studies have been exclusively performed in ill-defined matrices whose properties cannot be controlled. As such, the uncharacterized interactions between cells and this extracellular matrix have proven to be a major challenge to understanding the underlying regulatory mechanisms governing morphogenesis. In this talk, I will highlight our recent efforts to employ tunable synthetic hydrogels to disentangle the contributions of biochemical and mechanical effectors in specifying stem cell fate and self-organization.

Speaker

Synthetic biology unveils control principles of stochastic gene choice and mRNA turnover

Attila Becskei

Biozentrum, University of Basel, Switzerland

Synthetic biology has been increasingly employed to study cellular functions. We used synthetic transcription factors to explore the control principles in transcriptional and posttranscriptional processes. We identified a switch in the transcriptional regulatory logic during cellular differentiation. While a transcriptional activator targeted to a gene activates specifically the target gene in embryonic stem cells, it behaves like an enhancer by activating distant genes upon differentiation to neurons. At the same time, it introduces correlations in the stochastic gene choice by inducing an epigenetic gradient along the chromosome. To study posttranscriptional RNA turnover, we recruited synthetic activators and repressors to promoters, and found that the median half-life in yeast is only around 2 minutes, shorter than previously reported. The half-lives obtained with this method correlate only with one of the variants of the genome-wide, transcriptional inhibition and metabolic labelling, methods. Thus, synthetic biology can provide critical insight into and identify control principles of cellular processes.

Short talk | 10

A synthetic framework on membrane protein organisation modulated by feedback reactions

Rukmini Jonnalagadda, **Chieh Hsu**

Kent Fungal Group, School of Biosciences, University of Kent, Canterbury, United Kingdom

Synthetic biology, the discipline exploring life sciences by constructing molecular networks from basic modules, has successfully enhanced the understanding in gene regulation. However, the complexity of spatial molecular distribution makes it experimentally difficult to utilise synthetic approaches in cell biology. Here we illustrate a design to overcome these difficulties.

In eukaryotic cells, organelles exchange materials in vesicles in a process named membrane trafficking. To initiate correct sorting, a given membrane needs to be firstly identified by molecular switches, such as the Rab proteins, that shuffle between membrane and cytosol. A widely accepted hypothesis stating that positive feedback mechanism defines the localisation, stability and organisation of the membrane identifying process: recruitment of the molecular switch is self-activated by the same molecule on the membrane.

To investigate such process quantitatively, we built a synthetic model in Saccharomyces cerevisiae. We assembled positive feedback reactions centred around synthesis and catalysis of phosphatidylinositol (3,4,5)-trisphosphate (PIP3) and phosphatidylinositol (4,5)- bisphosphate (PIP2). The feedbacks reactions reflect the aforementioned membrane identifying processes and the parameters can be fine-tuned to study the individual contribution of sub-process.

We also established a florescence microscopic method to quantify the membrane PIP2/PIP3 levels, which does not only allow us to analyse the system's average status, but also enables single cell observation, including spatial distribution of certain components. With this system, we explore the dynamics of molecular translocalisation and interaction between feedbacks, which will shed lights on the key regulations in intracellular membrane trafficking.

Short talk | 26

Spatiotemporal Control of TGF-beta Signaling with Light

Yuchao Li[1], Minji Lee[2], Nury Kim[2], Guoyu Wu[1], Xuedong Liu[3], Won Do Heo[2], **Zhike Zi**[1]

[1]Max Planck Institute for Molecular Genetics, Berlin, Germany; [2]Department of Biological Sciences, Korea Advanced Institute of Science and Technology, Daejeon, Republic of Korea (South); [3]Department of Chemistry and Biochemistry, University of Colorado Boulder, Boulder, United States

Cells employ signaling pathways to make their decisions in response to changes in their immediate environment. Transforming growth factor beta (TGF-beta) is one of the most important growth factors that regulate many cellular functions in development and disease. Although the molecular mechanisms of TGF-beta signaling have been well studied, our understanding of this pathway is limited by the lack of tools that allow the control of TGF-beta signaling with high spatiotemporal resolution. Here, we developed an optogenetic system (optoTGFBRs) that allows precise control of TGF-beta signaling in time and space. Using the optoTGFBRs system, we show that TGF-beta signaling can be selectively and sequentially activated at the single cell level through modulating the pattern of light stimulations. By simultaneously monitoring the subcellular localization of TGF-beta receptor and Smad2 proteins, we characterized the dynamics of TGF-beta signaling in single cells. The spatial and temporal precision of light control will make the optoTGFBRs system as a powerful tool for quantitative analyses of TGF-beta signaling.

Poster | 33

Designing spatially linked microbial consortia: the assembly of misfits

Sami Ben Saïd, Dani Or
ETH Zurich, Switzerland

The metabolic diversity present in microbial communities and the specialization or division of labour allows spatially-organized microbial consortia to efficiently utilize resources and accomplish more complex tasks than possible by a single microorganism. Current biotechnological applications of microorganisms remain rudimentary often relying on genetically engineered monocultures (e.g. pharmaceuticals) or mixed-cultures of partially known composition (e.g. wastewater treatment). The vast potential of "microbial ecological power" remains largely underused. We propose to capitalize on ecological insights into the spatial and modular design of interlinked microbial consortia by engineering niches that would overcome limitations of natural systems to optimize conditions for members and the performance of the engineered consortium. The topology of spatial connections linking various members and the regulated media fluxes between modules would expand the possible range of members and interactions. The modularity of such spatially linked microbial consortia (SLMC) offers scalability of bioprocesses and their incorporation into larger biochemical networks. By reducing the need for a compatible growth environment for all species simultaneously, the SLMC will dramatically expand the range of possible combinations of microorganisms and their potential applications.

Poster | 122

Modeling and analysis of arsR genetic circuits

Yves Berset[1], Davide Merulla[2], Aurélie Joublin[2], Vassily Hatzimanikatis[1], Jan Roelof van der Meer[2]

[1]EPF Lausanne, Switzerland; [2]University of Lausanne, Switzerland

Bioreporters are genetically engineered cells that are able to respond to a specific compound with an easily measurable signal. Because cells are cheap to produce and can be integrated in microfluidic devices, bioreporter assays can potentially reduce the cost and facilitate the logistics for the measurement of toxic compounds. Several bioreporters based on the Escherichia coli ArsR system have been previously developed for the detection of arsenic, including strains with tunable response1. However, their performances were not optimized for the arsenic concentration limit recommended by the World Health Organization in drinking water (10 µg arsenite L-1). To better understand the key mechanisms of the bioreporters, we developed a comprehensive mathematical model that describes the building blocks of the different circuits (DNA, mRNA, proteins, complexes) and their detailed interactions (binding, synthesis, degradation, maturation) ultimately leading to the fluorescent response. The model parameters appear in two circuit topologies (feedback and uncoupled) and were estimated by scatter search to reproduce the experimental fluorescence measured at different arsenic concentrations. The parameter estimation was further constrained by available ArsR biochemical data. The resulting model2 is in agreement with feedback and uncoupled circuit configurations, different ArsR alleles and uncoupled promoter activities. Using sensitivity analysis, the model predicted a circuit variant with a steeper response curve at low arsenic concentrations. The strain was experimentally tested and may provide a useful arsenic bioreporter in the field.

Poster | 51

Metabolite toxicity promotes the evolution of substrate cross-feeding, but depends on initial frequencies

Jan Dolinšek[1, 2], David Johnson[1]

[1]Eawag, Swiss Federal Institute of Aquatic Science and Technology, Department of Environmental Microbiology, Dübendorf, Switzerland;
[2]Department of Environmental Systems Science, ETH Zurich, Switzerland

A typical feature of metabolic pathways is that they produce and potentially accumulate toxic intermediate metabolites. One plausible solution to this problem is substrate cross-feeding, whereby a second genotype specializes at consuming the toxic metabolite. We asked whether specialist genotype that consumes a toxic metabolite can invade into a genotype that completely performs the metabolic pathway.

Our model system is based on the denitrifying bacterium Pseudomonas stutzeri, which consumes nitrate to nitrogen gas but transiently accumulates the toxic intermediate nitrite. We constructed an isogenic mutant from this strain that cannot consume nitrate but can consume the toxic metabolite nitrite. We then assembled the two genotypes and asked whether they could coexist with each other.

We found that the completely consuming and specialist genotypes could invade into populations of the other, and co-exist via nitrite cross-feeding. Over the evolutionary timescales, however, the completely consuming genotype rapidly evolved streamlined metabolism where nitrite no longer accumulated, thus eliminating the niche space for the specialist to invade into. Our results demonstrate that metabolite toxicity promotes the evolution of cross-feeding, but this outcome depends on the initial frequencies. Thus, the frequency of one genotype can have profound effects on the evolutionary trajectories of other genotypes.

Poster | 135

Generation and analysis of large-scale dynamic nonlinear models of metabolism

Georgios Fengos, Ljubisa Miskovic, Vassily Hatzimanikatis
EPF Lausanne, Switzerland

Generation and use of large-scale kinetic models is hindered by the intrinsic nonlinearities of the enzymatic rate expressions, and the uncertainties at the level of concentrations and kinetic parameters. Here, we use the ORACLE framework, which is an efficient and scalable methodology for the generation of populations of large-scale, non-linear models of metabolism. With this approach, we can explore the properties of a system of biochemical reactions, their dynamic responses, and their potential to maintain a steady state upon perturbations. We can further analyze the effect of integrating data from thermodynamics, available omics, and kinetic data on these properties.

To demonstrate the utility and performance of this methodology we constructed a population of large-scale dynamical models of optimally grown E. coli that involves 239 metabolites and 285 reactions. We used these models to: (i) perform a modal analysis and characterize the parameters that are associated with biologically relevant time scales, (ii) identify and analyze multiple steady states, and (iii) characterize basins of attraction around the identified steady states. The aforementioned analyses provide valuable insights for the design of synthetic biology and metabolic engineering strategies towards the development of robust whole-cell biocatalysts for bio-sustainable economies.

Poster | 130

Exploring chemodiversity in metabolism towards the supervised integration of chemistry into biology

Noushin Hadadi, Jasmin Hafner, Homa Mohammadi Peyhani, Vassily Hatzimanikatis

Laboratory of Computational Systems Biotechnology (LCSB), EPF Lausanne, Switzerland

The availability of different levels of omics data helps us to observe cells with higher resolution and from different perspectives. However, complete understanding of metabolism lags behind in explaining the chemodiversity observed in living organisms – the known reactome does not account for the appearance of many metabolites.

We applied the computational tool BNICE.ch to build the "ATLAS of Biochemistry" using expert curated generalized enzyme reaction rules. The first version of ATLAS contains all possible reactions (known and hypothetical) between known biological compounds. In the extended version of ATLAS, we extrapolate the known metabolism towards the chemical knowledge space and we integrate in a supervised manner chemical compounds and their associated reactions into a super network of metabolism. We demonstrate that the supervised integration of chemicals into metabolic networks is the key to complete the mechanism of poorly characterized reactions and to integrate thousands of orphan metabolites into metabolic networks.

ATLAS is available as an online database (http://lcsb-databases.epfl.ch/atlas) and is equipped with additional data analysis tools. ATLAS can further be used to create hypotheses about the origin of experimentally measured compounds and serve as a tool for metabolic engineers, synthetic biologists and other scientists working with metabolomics and secondary metabolism.

Poster | 106

Characterization of bistability and transition rates in transcriptional positive feedback loops

Vincent Jaquet[1], Chieh Hsu[1, 2], Farzaneh Maleki[1], Mumun Gencoglu[1], Attila Becskei[1]

[1]Biozentrum, University of Basel, Switzerland; [2]School of Biosciences, University of Kent, Canterbury, United Kingdom

Bistability plays an important role in cellular memory and cell-fate determination. A positive feedback loop can generate bistability if it contains at least one ultrasensitive molecular reaction. Protein homodimerization is a ubiquitous ultrasensitive reaction, yet its role in bistability remained elusive. We designed feedback loops where we modulated homodimerization and cooperative promoter binding of the transcription factor. Either of them was sufficient to display bistability in hysteresis experiment. The hysteresis range cannot however, unequivocally map the bistable region because it shrinks over time. Therefore, we developed an approach to open the loops experimentally in order to identify a deterministic model. Noise in gene expression was the key determinant of the transition rates inside the bistable range. Transitions between two cell fates were also observed outside of the bistable range, evidenced by bimodality and hysteresis. In this case, a slow transient process was the rate limiting step in the transitions. Finally, combining the open-loop function with kinetic measurements and re-introducing the measured noise, we were able to predict the transition rates without parameter tuning. This overall approach can help to characterize a variety of complex molecular mechanisms such as the ones involved in cell differentiation and cellular memory of past stimuli.

Poster | 76

Synthetic methylotrophy – from understanding to engineering

Fabian Meyer, Jonas Müller, Johannes Hartl, Patrick Kiefer, Julia Vorholt
ETH Zurich, Switzerland

The ability to use methanol as sole carbon source makes methylotrophs interesting candidates for industrial applications. Due to the lack of genetic manipulation, the use of natural methylotrophs such as Bacillus methanolicus is limiting their potential in biotechnology. As an alternative approach, we aim at combining the potential of a methanol based metabolism with the genetic accessibility of Escherichia coli by engineering a synthetic methylotroph. Achieving this goal is combined with a deeper understanding of the system biological properties of natural methylotrophs. Performing metabolome analysis in the natural methylotroph B. methanolicus have been used to identify methylotrophic specific features needed to create an artificial methanol utilizing E. coli. We generated an engineered E. coli strain that is able to incorporate methanol into core-metabolites, up to 40% in case of hexose-6-phosphate. The incorporation of methanol was shown by using dynamic 13C labeling experiments starting from 13C methanol.

Poster | 82

Unlocking the full potential of kinetic metabolic models through characterisation and reduction of uncertainty

Ljubisa Miskovic, Vassily Hatzimanikatis

Laboratory of Computational Systems Biology (LCSB), EPF Lausanne, Switzerland

Kinetic models are the most promising tool for comprehending the complex dynamic behavior of living cells. The primary goal of kinetic models is to capture the properties of the metabolic networks as a whole, and we need large-scale models for dependable in silico analyses of metabolism. However, the uncertainty in kinetic parameters is the main obstacle hindering the development of kinetic models, and the levels of uncertainty increase with the size of the models. Therefore, there is a need for tools that will address the issues with the uncertainty in parameters, and that will be able to reduce the uncertainty propagation through the system. In this work, we employed a method called iSCHRUNK that combines parameter sampling and parameter classification techniques to characterize the uncertainties and to uncover intricate relationships between the parameters of kinetic models and the responses of the metabolic network. The proposed method allowed us to identify only a few parameters that determine the responses in the network regardless of the values of other parameters. As a consequence, in future studies of metabolism, it will be sufficient to explore a reduced kinetic space, and more comprehensive analyses of large-scale and genome-scale metabolic networks will be computationally tractable.

Poster | 132

Evaluating the similarity of biochemical reactions and its uses for mapping novel reactions to protein sequences

Homa Mohammadi Peyhani, Noushin Hadadi, Vassily Hatzimanikatis

Laboratory of Computational Systems Biotechnology, EPF Lausanne, Switzerland

A key challenge in metabolic engineering is to design novel or to improve existing biosynthetic pathways that lead to the cellular production of a given industrial or pharmaceutical compound. In many cases, the required enzymatic reactions for the biosynthesis of the target molecule need to be designed from scratch. BNICE.ch is a method that enables the design of de novo synthetic pathways through the postulation of novel biotransformations. However, finding enzymes that can potentially catalyze the proposed reactions remains a challenge. In this work, we propose a novel method, named BridgIT, to link novel reactions with well characterized enzymatic reactions and their associated genes. BridgIT compares every predicted novel reaction to all known enzymatic reactions for which a protein sequence is available. Novel and known reactions are compared based on the similarity of the reactive site of the substrates and the breakage and formation of atomic bonds during the conversion of the substrate to the product. As a result, BridgIT reports a similarity score for each comparison of known reactions to novel reactions, thus giving an estimate of the likelihood that a given enzyme can catalyze a novel reaction. The candidate proposed enzymes for de novo reactions by BridgIT, are either capable of catalyzing these reactions or they can serve as good initial sequences for the enzyme engineering. BridgIT online tool is freely available on the web (http://lcsb-databases.EPF Lausanne.ch/) for academia upon subscription.

MetaNetX/MNXref release 3: Major improvements in the reconciliation of metabolites and biochemical reactions to ease metabolic network reconstruction.

Sébastien Moretti[1], Olivier Martin[1], Alan James Bridge[2], Marco Pagni[1]

[1]Vital-IT group, SIB Swiss Institute of Bioinformatics, Lausanne, Switzerland;
[2]Swiss-Prot group, SIB Swiss Institute of Bioinformatics, Geneva, Switzerland

MetaNetX (http://www.metanetx.org) is a web site that provides tools to create, analyse and compare genome-scale metabolic networks. It is built on top of a repository of genome-scale metabolic networks and biochemical pathways imported from major public resources into a common namespace of chemical compounds, reactions, cellular compartments and proteins.

The new release of the MNXref namespace brings improvements in the reconciliation algorithm, as well as new data sources:

- The use of molecular structures to reconcile chemical compounds was systematised
- Biochemical and transport reactions are now described with their metabolites placed into generic compartments
- Two new data sources have been added: SABIO-RK and SwissLipids
- Previous data sources have been updated: BiGG, ChEBI, EnviPath, HMDB, KEGG, LipidMaps, MetaCyc, Reactome, Rhea and TheSEED

This project was developed in close collaboration with the RHEA and SwissLipids teams in Geneva and benefitted from tightly coupled release cycle and correction with international resource providers that either use or embed MetaNetX reference dataset.

A cloud-based service for the automated creation of genome-scale metabolic network model from a microbial genome

Sébastien Moretti[1], Thuong Van Du Tran[1], Frédéric Burdet[1], Louise Lefrançois[2], Mathias Ganter[3], Ove Øyås[3], Thierry Soldati[2], Jörg Stelling[3], **Marco Pagni**[1]

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A genome-scale metabolic network (GSMN) is a set of biochemical and transport reactions in an organism, associated with their protein catalysers and the genes encoding them. A GSMN has a double purpose, as it is both a repository of knowledge about an organism's metabolism, and a model that can be simulated, using flux balance analysis (FBA) for example. We are proposing here a fully automated web service to create a GSMN given an organism's genome. This service was built on top of original algorithms and databases developed during the MetaNetX project (SystemsX.ch). The quality of the automatic reconstruction was benchmarked against experimental data for different organisms. In the framework of the HostPathX project (SystemsX.ch), a GSMN was constructed for Mycobacterium marinum. Gene essentiality was predicted through simulation of single gene knockout mutants and compared against experimental results from transposon mutagenesis experiments in different growth conditions. Our GSMN for M. marinum harbours a predictive power which is comparable to what is achieved by manually-curated GSMN for M. tuberculosis.

Poster | 107

A synthetic double repressor circuit for the detection of interactions between transcription factors and their binding sites

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Synthetic biology offers powerful tools to study protein-DNA interactions. Here, we present a synthetic circuit to identify the DNA binding sites of a transcription factor (TF) of choice. We call our circuit the “double repressor”: the binding site to be screened is cloned downstream of a constitutive promoter, which is located upstream of an operon that codes for both the Lac repressor (LacI) and the red fluorescent protein mCherry. In turn, LacI regulates the transcription of the green fluorescent protein (GFP), because its binding site (lacO) is placed downstream of the promoter responsible for GFP expression. Thus, LacI represses GFP transcription, unless the TF interacts with its binding site, in which case LacI production is repressed and GFP is expressed. As a result, the presence of green fluorescence indicates the binding of the TF to the DNA binding site under investigation. Our system, once transformed into E. coli, facilitates the screening of libraries of TF binding sites and the isolation of cells where the TF is bound (green fluorescence). This is achieved using fluorescence -activated cell sorting (FACS). In future work, we will use this circuit to study the evolution of TF-DNA interactions.

Poster | 74

Model discrimination through optimal experimental design

Francesca Parise[1], Jakob Ruess[2], **Eve Tasiudi**[3], John Lygeros[3]

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The synergy of mathematical modelling and experimentation has provided critical knowledge on biochemical networks; however, ambiguities still remain. Despite the advancement of quantitative experimental techniques, networks may be too complex, stochastic and only partially structurally and parametrically determined. Moreover, resolving these uncertainties based on mathematical models has to be based on noisy data. Given a collection of possible models describing the network, the question that arises is, how sure can we be about the identity of the data-generating model after observing the data? Going a step back and designing effective and informative experimental conditions that provide maximal discriminatory power among the models before obtaining the data is valuable not only in terms of mechanistic insight but also in terms of the time and cost of the experimental study. Here, we employ an optimal design method for inferring the most plausible model and its parameters from a class of models. For a given experiment, we measure the average distance of the prior predictive distribution for each model to the mixture of all hypothesized models. Then from a set of possible experiments we search for the one that maximizes the value of dissimilarity of the model predictions, thus has the best chance of successful discriminating the models. These methodological developments developed under the SignalX project are being validated on data for TOR signaling and GATA factor gene regulation.

Poster | 18

Cooperation controls partners spatial intermixing in a synthetic bacterial consortium

Robin Tecon, Dani Or

Department of Environmental Systems Science, Soil and Terrestrial Environmental Physics, ETH Zurich, Switzerland

Microbes are essential actors in all environments (nutrients cycling, pollutants bioremediation, and more), and their functions depend on multispecies communities that possess intricate interspecies interactions and high degree of spatial organization. Due to the complexity of natural microbial systems, mechanistic understanding of community spatial assembly and activity remains fragmentary. Here, we used a synthetic ecology approach to ask how simple factors such as carbon utilization control spatial patterns of a two-partner bacterial consortium grown on surfaces. The experimental model consortium consisted of two mutant strains of Pseudomonas putida that cooperate to degrade and utilize toluene. Strains tagging with different autofluorescent proteins allowed for microscopic visualization and pattern quantification by image analysis. We showed that trophic cooperation (toluene degradation) led to convergence of partner abundance (1:1) regardless of the initial ratio, and to strong strain intermixing at the microscale (10-100 microns). In contrast, competition for a carbon source (benzoate) degraded independently by both strains resulted in distinct segregation patterns. The consortium productivity (cell growth) on toluene was affected by the initial partner ratio on surfaces but not in liquid cultures. This study pinpoints general principles of microbial community spatial organization with potential applications for natural and engineered microbial systems.

Poster | 120

Discovery, evaluation and analysis of novel pathways for production of five methyl ethyl ketone precursors

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EPF Lausanne, Switzerland

The limited amount of fossil fuels shifted research in industry and academia towards sustainable production of their substitutes. One of the most prominent biofuel candidates is Methyl Ethyl Ketone (MEK), due to its thermo-physical and transport properties. Since there is no native producer of MEK, we used Biochemical Network Integrated Computational Explorer (BNICE.ch) to explore the space of biotransformations around it. Out of 1325 identified compounds one reaction step away from MEK we chose 5 for further study as they can be (i) chemically converted to MEK; (ii) used as precursor metabolites for other chemicals. We reconstructed 3'679'610 novel biosynthetic pathways up to 4 reaction steps from 157 central carbon metabolites of E. coli toward these 5 compounds, and we retained the set of 18'925 biologically viable pathways based on their bioenergetics feasibility and yields. For each novel reaction in the viable pathways, we proposed the most similar KEGG reactions and their gene sequences as candidates for either a direct experimental implementation or enzyme engineering. Furthermore, we classified feasible pathways depending on the reactions and precursors that were essential for production of the target molecules. This study shows the potential of BNICE.ch for future synthetic biology and metabolic engineering studies.

Physics of Living Systems

Chair:
Félix Naef
Computational Systems Biology Lab
EPF Lausanne

Speaker

Diversity of immune receptor repertoires

Aleksandra Walczak

Ecole Normale Supérieur, France

Recognition of pathogens relies on the diversity of immune receptor proteins. Recent experiments that sequence the entire immune cell repertoires provide a new opportunity for quantitative insight into naturally occurring diversity and how it is generated. I will show how applying statistical inference to recent experiments that sequence entire immune repertoires we can quantify diversity of this functional ensemble and sharing of repertoires between individuals.

Speaker

Upside Down and Inside Out: The biomechanics of cell sheet folding

Ray Goldstein

University of Cambridge, United Kingdom

Deformations of cell sheets are ubiquitous in early animal development, often arising from a complex and poorly understood interplay of cell shape changes, division, and migration. In this talk I will describe an approach to understanding such problems based on perhaps the simplest example of cell sheet folding: the “inversion” process of the algal genus Volvox, during which spherical embryos literally turn themselves inside out through a process hypothesized to arise from cell shape changes alone. Through a combination of light sheet microscopy and elasticity theory a quantitative understanding of this process is now emerging.

Speaker

Exploring the generation and coordination of forces driving dorsal closure during Drosophila embryogenesis

Damian Brunner

Department of Molecular Life Sciences, University of Zurich, Switzerland

We use the fruit fly *Drosophila melanogaster* as a model organism to investigate the molecular mechanisms and cell shape changes that generate the forces driving tissue morphogenesis. We focus on dorsal closure a wound healing-related process taking place in mid-embryogenesis. During dorsal closure an eye-shaped gap in the dorsal embryonic epidermis closes. The process begins when the two epidermal cell sheets that laterally flank the opening, start converging dorsally. When their leading fronts have sufficiently approached, the corresponding cells on both sides recognize each other and fuse. Fusion activity starts at the anterior and posterior corners of the opening, from where it moves across the gap similar to closing zippers.

Closure involves the formation of a contractile, supra-cellular actin cable that surrounds the opening. Until recently, this cable was believed to produce a substantial force that alone can drive the closure process. In addition, the amnioserosa cells that fill the epidermis opening, provide a second force that can drive epidermis closure in an autonomous fashion. Slow, gradual apical constriction of the amnioserosa cells, which is superimposed on an intriguing rapid pulsing behavior, produces this force. Our recent data, collected using new protein interference technology and live imaging, show that the key force is exclusively being produced by the amnioserosa tissue while the epidermal actomyosin cable does not contribute. I will present data showing how we address the complex and highly dynamic behavior of this key tissue using a finite element modelling approach that combines biochemical reaction diffusion systems and mechanical aspects of amnioserosa cell behavior. The model predicts the emergence of the previously observed, patterned apical constriction of amnioserosa cells, which so far this was thought to be controlled by signaling gradients.

Speaker

Nanopores in 2D materials

Aleksandra Radenovic

Laboratory of Nanoscale Biology, EPF Lausanne, Switzerland

In this talk I will address novel applications ranging from identification of single nucleotides, but as well go beyond DNA sequencing and provide effective ways for DNA mapping and barcoding. To identify or barcode DNA, we use novel solid state nanopore platform based on atomically thin nanopore membranes in 2D materials such as graphene or molybdenum disulfide for DNA detection, sequencing, water desalination and osmotic power generation.

A Living Mesoscopic Cellular Automaton Made of Skin Scales

Anamarija Fofonjka[1, 2], Liana Manukyan[1, 2], Sophie A. Montandon[1], Stanislav Smirnov[3, 4, 5], Michel C. Milinkovitch[1, 2]

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In vertebrates, skin colour patterns emerge from non-linear dynamical microscopic systems of cell interactions. Here, we show that skin colour in ocellated lizards contrasts with this framework as a quasi-hexagonal lattice of skin scales establishes a green and black labyrinthine pattern. We analysed lizard colour dynamics over four years of their development and demonstrate that the pattern is produced by a cellular automaton (CA) that dynamically computes the colour states of individual mesoscopic skin scales, hence the corresponding macroscopic colour pattern. Using numerical simulations and mathematical derivation, we identify how a discrete von Neumann CA emerges from a Turing continuous reaction-diffusion (RD) system: skin thickness variation generated by skin scale 3D morphogenesis causes the underlying RD dynamics to separate into microscopic and mesoscopic spatial scales, the latter generating a CA. Our study indicates that the fundamental concept of CAs, as abstract computational systems, is an actual process generated by biological evolution.

Rules of thumb in gene control: optimality and suboptimality of a bacterial growth law

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[1]Friedrich Miescher Institute, Basel, Switzerland; [2]Weizmann Institute of Science, Rehovot, Israel

Organisms adapt their gene expression to improve their fitness in diverse environments. But finding the optimal gene expression in all environments may be an unsolvable task, or at least require regulatory mechanisms that are so expensive that they reduce fitness. We asked how good cells are at finding such optimal gene expression by studying the control of carbon catabolism genes in E. coli. The growth rate that bacteria reach on different carbon sources declines linearly with the steady-state expression of carbon catabolic genes, a relation known as a bacterial growth law. We experimentally modulated gene expression to ask if this growth law always maximizes the growth rate, as has been suggested by theory. We found that the growth law is optimal in many conditions, including a range of perturbations to lactose uptake, but provides suboptimal growth-rate on several other carbon sources. Combining theory and experiment, we genetically re-engineered E. coli to make sub-optimal conditions into optimal ones and vice-versa. We concluded that the carbon growth law is not always optimal, but represents a rule-of-thumb: a practical heuristic that often works but sometimes fails. We speculate that rules-of-thumb allow organisms to make complex computations at a practical cost.

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Physical Model of Host-Virus Interactions in Influenza Virus Capsid Disassembly

Alina Artcibasova, Jörg Stelling
D-BSSE, ETH Zurich, Basel, Switzerland

Emerging antiviral drug resistance complicates the treatment of influenza and other viral infections. Many antiviral drugs directly bind to the target viral protein and prevent viral replication. Such a mechanism of action creates evolutionary pressure on the virus, and eventually most viral strains carry mutated, drug-resistant versions of the target protein. New drug development efforts target host proteins that play important roles in viral replication.

It is hypothesized that influenza virus mimics misfolded protein aggregates by carrying unanchored ubiquitin (Ub) chains. Ub attracts histone deacetylase 6 (HDAC6), which recruits molecular motors dynein and myosin II. They then pull protective capsid apart and release the viral RNA. Thus, HDAC6 might be a suitable host drug target against influenza.

To quantitatively test feasibility of this mechanism, we developed a novel physical model of influenza capsid disassembly. Ordinary differential equations describe a core system of physical interactions between capsid protein, Ub, HDAC6, dynein and myosin II. Our analysis of capsid disassembly probabilities depending on system parameters (e.g., motors numbers, energy and stiffness of bond between capsid proteins) suggests that myosin II plays the main role in capsid disassembly, but small dynein inclusions make disassembly more efficient, which is consistent with experimental findings.

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Mechanochemical modelling as an explorative tool to study Drosophila dorsal closure

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Dorsal closure is a morphogenetic process in Drosophila embryogenesis, whereby an epidermis opening closes. The epidermal opening is filled with the Amnioserosa (AS) tissue, which drives dorsal closure by apical constriction of its individual cells. Apical constriction in turn is driven by apical surface area oscillations, the result of periodically forming, transient actomyosin foci. We use reaction-diffusion equations to model these foci at the subcellular level in 2D in a finite element implementation. Thereby, actomyosin concentration determines the strength of contraction. Further, we assume that the surrounding epidermis adapts in response to the pulling force of the AS tissue, as shown experimentally. Mechanical forces and the resulting material deformation are calculated using a superimposed finite element discretisation. Our simulations reproduce dorsal closure and make clear predictions that ask for experimental testing. In particular, a sequential arrest of cellular oscillations simply emerges, similar to what was observed in vivo. So far, a dpp-signalling gradient was thought to control this phenomenon. Addressing this experimentally confirmed the model prediction. Interestingly, 3D finite element simulations predict that the emerging sequential pulsation arrest generates a contractility gradient, which controls AS tissue morphogenesis.

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Modelling the Developing Limb

Diana Barac[1], Erkan Ünal[1, 2], Zahra Karimaddini[1], Rolf Zeller[2], Dagmar Iber[1]

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The limb is a model system for studying development. However, although the main molecules that are known have been studied extensively, in “in vitro” or “in vivo” systems, most research has focused on the effect of a single protein rather than the regulatory network as a whole. Through building a computational model of limb development, we hope to integrate the core networks and gain insight into how they interact and work together. For example, we can study the effect that changing one component has on others, or how this impacts gene expression patterns at a specific developmental time point. By utilising 3D limb bud shapes from mouse and chicken embryos, obtained by previous members of our group, our integrative model can be simulated on realistic domains.

A key challenge in modelling is estimating parameters. In the case of the “in silico” limb model, this is particularly relevant due to the large number of parameters and high computational cost. We aim to develop a pipeline for automatic parameter inference.

Once completed, our model will be continuously validated against new data, and subsequently used to explore mutant phenotypes as well as examine the impact of geometry on pattern formation.

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Growing under pressure: microbial growth rates under physical confinement

Samuel Bickel, Dani Or
ETH Zurich, Switzerland

Microbial cells growing in ocean sediments and soil are frequently confined in pore spaces and limited by nutrient fluxes. Growth characteristics of microbial populations are often studied in batch liquid cultures or on agar surfaces to derive predictive kinetic physiological parameters. Such conditions may be far removed from growth kinetics experienced in natural settings. Recent findings suggest that microbial growth is limited not only by nutrients but also by pressures across the cellular membrane that reduce growth rates with increasing external pressures. We developed an experimental platform for direct measurement of the pressure exerted by a confined microbial colony under controlled nutrient supply. We report the decrease of growth rate with increased applied pressures and estimate growth kinetics of confined microbial colonies under varying nutrient conditions (supplied via rigid porous surfaces). Preliminary estimates from measurements with confined Saccharomyces cerevisiae colonies suggest that effective growth rates are almost halved with an increase in pressure of 0.1MPa (from about 0.1h-1 to 0.05h-1). Results offer realistic growth parameters considering environmental mechanical pressure encountered in situ where space and nutrients are of limited availability.

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Interplay between Notch signaling and ID factors during adult and embryonic neurogenesis

Marcelo Boareto[1], Dagmar Iber[1], Verdon Taylor[2]

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During neurogenesis, multipotent neural stem cells (NSCs) give rise to the correct number and types of neurons. Notch signaling and inhibitor of DNA binding (ID) factors are recognized as pivotal during neurogenesis, however it has been difficult to evaluate experimentally the underlying mechanism of their interactions and the differences between embryonic and adult neurogenesis. We combined mathematical modeling with single-cell transcriptomics to elucidate key interactions between the Notch and ID pathways in embryonic and adult NSCs. We show how both pathways regulate neurogenesis in a complementary and independent manner in the adult brain. In contrast, during brain development, Notch signaling directly regulates the expression of IDs and this regulation precludes ID-induced quiescence. Our analyses unveil key molecular interactions underlying NSC quiescence, maintenance and differentiation, highlighting mechanistic differences between embryonic and adult NSCs. Similar mechanisms are expected to be critical in other stem cell systems during development and disease.

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Combining MEMS force-sensing and microfluidics: Mechanical characterization of living plant cells

Jan Burri[1], Hannes Vogler[2], Nino Läubli[1], Gorka Santos[2], Chengzhi Hu[1], Ueli Grossniklaus[2], Bradley Nelson[1]

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Understanding the mechanisms of plant growth and morphogenesis is of importance, not only to the field of plant sciences but also in a broader agricultural and economical context, as plants provide important raw materials such as food, fiber, wood and fuel. Mathematical modeling and simulation can provide insights into intricate biomechanical growth mechanisms. Mechanical characterization at the single cell level is essential for providing quantitative model parameters. The Cellular Force Microscope (CFM) provides such parameters by micro-indentation measurements, integrating MEMS force-sensing technology with a piezoelectric nano-positioning system. Interfacing the CFM with microfluidic platforms and Lab-on-a-Chip (LoC) devices improves the throughput of the experiments, facilitates microscopic observations and opens up new possibilities to study the influence of mechanical and chemical cues. The free design of microfluidic devices can be tailored to various tasks and to the scale and shape of each specimen. Different configuration of microfluidic platforms were used to characterize the mechanical properties of Lilium longiflorum and Arabidopsis thaliana pollen tubes (diameter ≈ 17 um resp. 6 um), as well as Brachipodium distachyon roots (diameter ≈ 400 um).

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Dynamic phosphorylation of the budding yeast kinesin Kip2 regulates the interplay between Kip2, Bik1, and Bim1 to control the length of astral microtubules

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The microtubule cytoskeleton is a dynamic structure, yet the average length of the microtubules is tightly controlled. At the microtubule +end, the interplay between microtubule binding proteins, motors, and kinases is poorly understood. Kip2 is a cytoplasmic Kinesin-7 involved in stabilizing astral microtubules (aMTs). The mechanism by which this is achieved in vivo is unclear. Here we present a study of the regulation of Kip2 activity in stabilizing aMTs by quantifying the three dimensional (3D) length and dynamics of aMTs in vivo. We demonstrate that the Dbf2 dependent phosphorylation of the N-terminal region of Kip2 inhibits Kip2 activity and the C-terminal tail is essential for Kip2 functions. Further dissection of the Kip2 tail demonstrates it is required for the direct interaction with Bik1 both in vitro and in vivo. This interaction allows Bik1, together with Bim1, to retain Kip2 on growing and shrinking +ends, thus ensuring the stabilization of aMTs. Furthermore, we found that phosphorylation of Kip2 N-terminus inhibits its activity by negatively regulating the Kip2-Bik1 interaction. We developed a quantitative computational model for the regulation of aMT length by Kip2 and its phosphorylation, Bik1, and Bim1. Our data suggest that the dynamic regulation of Kip2 phosphorylation, thus the Kip2-Bik1-Bim1 interaction on +ends, contributes to control of aMT length and organization.

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Temporal fluctuations destabilise interactions in spatially structured microbial populations

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Introduction: Every natural microbial community is exposed to temporal fluctuations in their local environment, and they have developed many strategies to survive and adapt to such fluctuations. These perturbations can have profound effects not only on individual cells, but also on spatial self-arrangement and emergent community-level behaviors.

Objectives: Our goal was to understand the consequences of temporal environmental fluctuations on spatial self-arrangement of microbial assemblages and the ability of the assemblages to maintain productivity over time.

Methods: Our model system is based on two cross-feeding isogenic mutant strains of P. stutzeri A1501 that differ in their ability to reduce nitrate and nitrite. The two strains interact competitively for space and oxygen under aerobic conditions, but interact mutualistically via nitrite cross-feeding under anaerobic conditions.

Results: Stronger mutualistic interactions (via experimentally increasing the strength of nitrite toxicity) enhanced growth-coupling of the consumer and producer. This increased spatial intermixing of the two genotypes and provided the system, resulting in increased resilience to the temporal environmental fluctuations and increased productivity.

Conclusion: Temporal environmental fluctuations have profound effects on spatial self-arrangement and productivity and, under certain conditions, on the long-term persistence of microbial ecosystems.

Poster | 6

Detecting allosteric interactions in vivo using esterified metabolites

Maren Diether, Uwe Sauer
ETH Zurich, Switzerland

During the last decade, experiments have revealed several regulatory metabolites that are thought to modulate the activity of metabolic enzymes and signaling proteins. However, methods to study the effects of these metabolites in vivo remain elusive. We suggest that the cellular targets of regulatory metabolites can be revealed by perturbing their intracellular concentration and monitoring the consequences on metabolic enzyme activity and protein-phosphorylation. By screening a set of candidate metabolites, we aim at identifying new enzymatic targets and at obtaining a better understanding of cellular signal processing. So far, no method for the specific alteration of intracellular metabolite levels is available.

Here, we show that esterified metabolites can be used to specifically increase the intracellular concentration of selected metabolites in S. cerevisae. By monitoring the dynamic behaviour of intracellular metabolites upon ester treatment, we identify a set of responsive metabolites and recover previously known allosteric interactions.

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How can two biological oscillators synchronize? A study of the cell-cycle influence on the circadian clock

Colas Droin, Eric Paquet, Félix Naef

Computational Systems Biology Lab, EPF Lausanne, Switzerland

Coupled biomolecular oscillators are not only of great biological importance, but also very interesting from a dynamical systems point of view. In a systems biology context, the interconnection between two periodic processes such as the circadian rhythm and the cell cycle represents an ideal system analyzable at the single-cell level. The analysis of a large dataset from time-lapse imaging of single mouse fibroblasts showed, in previous studies, that circadian and cell cycles are robustly synchronized. This synchronization state is observed over a wide range of conditions resulting from a predominant control of the circadian clock by the cell-cycle. Here, we present a new method of inference based on a probabilistic model of the raw signal traces followed by parameter optimization using an expectation-maximization framework to reconstruct the phase dynamics. This new characterization of the coupling function should be of great help to make more rigorous predictions on cellular events that influence the circadian clock.

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Feedback, trafficking and morphogen scaling

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During development, embryonic tissues develop into organs of stereotyped size and shape. Morphogens are secreted from discrete regions in developing organs and form spatial concentration gradients that guide gene activation, pattern formation and tissue growth. Morphogen gradients scale with tissue size, ensuring that morphological patterns remain proportionate in organs of different size. How key molecular players ensured morphogen scaling is not clear. Motivated by our observations of the BMP-type growth factor Decapentaplegic (Dpp) in the fly wing, we explore the potential role of local feedback driven by Dally/Dpp interactions in morphogen scaling.

Poster | 3

Complex-centric proteome profiling by SEC-SWATH-MS: Quantitative insight into the modular proteome

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The assembly of gene products into complexes as functional units is key to cellular functions. Analyzing the vast protein complex landscapes of cellular systems at high throughput has been advanced by mass spectrometry-based protein elution profiling approaches, which, however, typically require separation along multiple chromatographic dimensions to attain specificity in complex detection in the context of low chromatographic resolution and limited precision in quantitative readout of elution profiles via DDA-based MS strategies.

To improve on this situation, we devised a DIA/SWATH-MS- and high resolution size exclusion chromatography-based workflow to generate complexomic maps at high definition. The integrated workflow comprises a novel, complex centric data analysis strategy, extending concepts of peptide-centric analysis of DIA/SWATH-MS data to the level of complex inference in SEC-SWATH-MS and thereby generates a comprehensive and accurate view on the cellular protein complex landscape. Using prior information on proteome connectivity enables high specificity in the error-controlled workflow to detect and quantify hundreds of protein complexes and -variants resolved chromatographically from the HEK293 cell line. We demonstrate the identification of a putative trimeric Mini-COP9 Signalosome and interesting insight from differentially mapping the protein complex landscape of the HeLa CCL2 cell line along cell cycle progression.

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Learning quantal parameters through expectation-maximization

Emina Ibrahimovic

ETH Zurich, Switzerland

Large synapses, i.e the neuromuscular junction (NMJ) or the calyx of Held, have been invaluable model synapses that have significantly advanced the field of synaptic transmission. However, no generative model approach can retrieve quantal parameters from synapses with a large number of release sites (N). We propose an expectation maximization (EM) algorithm that is based on particle smoothing (PS) to extract quantal parameters from large N synapses. Existing generative models scale with a complexity of N^4 and cannot retrace quantal parameters of synapses with hundreds of release sites. The complexity of our method is independent of N and therefore better suited for large synapses. First, our model was validated on synthetic data. Next, we applied the model to the Drosophila NMJ, which harbors around 600 release sites. The model-predicted quantal parameters are in line with parameters estimated by two empirical approaches (variance-mean analysis and cumulative amplitude analysis of postsynaptic currents). In contrast to these two techniques, which require data recorded under restricted conditions, such as a high release probability (p), our method is independent of p or stimulation protocol. Given the genetic tractability of this synapse, our theoretical approach is expected to help linking quantal parameters to molecular function.

Poster | 30

Evidence for tensile fracture patterning on the skin of the African elephant (Loxodonta Africana)

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When considered at the scale of the centimeter, the skin of the African elephant (Loxodonta Africana) exhibits an intricate network of narrow 'channels'. Previous studies have hinted at the adaptive value of such structures for water and mud retention, but their morphological characterisation and generative mechanism have remained largely unexplored. Here, we use a combination of histology, light and electron microscopy, image analyses and computed tomography (CT) to show that these features are discontinuities in the thick stratum corneum of the animal's epidermis. Moreover, the morphology of these gaps suggests that they constitute tensile fractures, i.e., they are generated by physical cracking. We use this evidence to propose a model for the formation of the 'channel' network, and we test the model with numerical simulations. While other instances of animal skin cracking have been reported in both normal and pathological conditions, this is the first described case in which this patterning mechanism is associated with a functional morphology.

Vertex Model of Cell Monolayers and its Applications

Aziza Merzouki[1], Orestis Malaspinas[1], Athanasia Tzika[2], Anastasiya Trushko[3], Guillaume Rapin[4], Patrycja Paruch[4], Aurélien Roux[3], Michel Milinkovitch[2], Bastien Chopard[1]

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We develop a vertex model of confluent cell monolayers, inspired from the model of Farhadifar et al. 2007. In this model, cells are represented by polygons and neighbor cells share common edges. Cells are characterized by their mechanical properties. They can proliferate and undergo topological rearrangements. Our model differs from that of Farhadifar by its time dynamics and boundary conditions. It is driven by Newton dynamics and open boundary conditions are implemented. We also allow different types of cells to co-exist and interact. In particular, a signal can be produced by one type of cells, be propagated through the tissue, and control the proliferation of a second type of cells. Moreover, the simulated tissue can be subjected to external mechanical constraints. The general purpose of this model is to study the influence of cell biophysics on tissue mechanics and morphogenesis. We study how cell physical properties affect the mechanical response of tissues to stretching, and inversely how tissue stretching may affect cell mechanical properties (Merzouki et al. 2016). We also analyze how cell biophysics influence tissue buckling and cell front progression. Finally, we use our model to study the morphogenesis of Acomys' spiny hairs follicles (Montandon et al. 2014).

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Mechanistic insight in ESCRT-III membrane remodeling

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The Endosomal Sorting Complex Required for Transport (ESCRT)-III mediates membrane deformation and scission in different cellular contexts, such as multivesicular body formation, cytokinesis, viral budding, plasma membrane repair, nuclear envelope sealing and more. However, mechanistic insight in how these proteins remodel membranes is scarce. Using a combination of in vitro techniques and electron microscopy (EM), we have found that two ESCRT-III proteins (Vps2 and Vps24) can co-assemble on protein polymers formed by Snf7, the major ESCRT-III protein. This co-assembly leads to the formation of a second, parallel polymer strand made of Vps2 and Vps24. Recruitment of Vps2 and Vps24 is also required for the AAA ATPase Vps4 to interact with the ESCRT-III proteins and to activate its ATPase activity, which results in remodeling of the ESCRT-III heteropolymer. Both ATPase activation and filament turnover coincide with membrane deformation as observed by dynamic light scattering and EM, indicating that they are necessary for ESCRT-III membrane remodeling, and having identified its minimal requirements allows us to further characterize this process structurally.

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3D shape of cells over time – Single cell analysis using Flybow

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The overall shape of organisms is defined during development. 2-dimensional (2D) studies have explored how cells change their shapes to infer how forces are generated during tissue development. However, how cells and tissues deform in 3 dimensions (3D) to originate variable shapes is still a fundamental question in biology. We use *Drosophila* embryogenesis to first characterize changes in individual cell 3D shape, if and how cells coordinate their shape changes and reveal the impact of those on tissue morphogenesis.

To study cell and tissue morphogenesis, we use a morphogenetic process called dorsal closure (DC). Amnioserosa (AS) cells fill the dorsal opening, pulse and progressively reduce their apical area to close the opening. However, until now it was challenging to image and resolve in space and time individual cells in 3D.

In this research project, we genetically label cells with four different membrane-tethered fluorescent proteins based on the Cre random recombinase-dependent excision of floxed genes, *Flybow*. We combine the multicolour cell labelling approach with either confocal or with multiview light-sheet microscopy for rapid imaging and minimal toxicity. Preliminary data shows that AS cells undergo dramatic 3D shape and different dynamics of apical and basal areas. Moreover, AS cells show interesting delamination shape changes and reveal an alternative delamination process mediated by yolk.

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An imaging-based systems biology approach to study the behavior of immune cells in intravital 2-photon microscopy

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Recent advances in microscopy technology have allowed the study of cell behavior in vivo, revealing unprecedented spatiotemporal dynamics of host-pathogen interaction. However, mining the mechanisms of the immune system from imaging data requires proper methods to be developed. Challenges arise from the complex biomechanical properties of immune cells, which exhibit high plasticity and frequent contacts during interstitial migration. Additionally, shapes appear with a blurred and fluorescent aspect that lacks constant color features and textures. Lastly, unavoidable technical artifacts are introduced during image acquisition. These difficulties limit the automatic analysis of cell movement with state of the art object detection and tracking algorithms. In this work, we developed a novel method that represents the microscopy scene as a hierarchical and space-time connected graph. Such a data structure provides a description of the observed phenomena from a single pixel to a system level and allows the prediction of the movement of immune cells and their tracking by solving a global optimization problem. Preliminary results on biologically relevant case studies showed an increased accuracy and robustness with respect to the state of the art imaging analysis pipeline. In conclusion, a database of microscopy videos with manually tracked cells, namely LTDB, was created and made available to the scientific community. LTDB is expected to be used as a sound ground truth for quantitative algorithm validation and represents a step towards big-data immunological research.

Poster | 57

Acid growth theory – A fundamental concept of plant development revisited

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Plant organogenesis is initiated from discrete meristematic stem cell pools that form the shoot and root systems. It is shaped by cell division and expansion, whose coordination is crucial because plant cells are surrounded by a cell wall that restricts cell movement. This cell wall consists of cross-linked polysaccharide polymers that resists the internal turgor pressure of plant cells. Thus, cell wall stiffness / elasticity limits growth processes and has to be regulated to allow cell expansion. Because key polymers are typically arranged in parallel, most cells expand anisotropically along one principal axis. Such cell elongation is paramount in organogenesis as well as in adaptive responses, and can be triggered by various plant hormones. Generally, it is assumed that this occurs through induction of genes that encode cell wall remodeling factors, such as expansins. Among those hormones, auxin has a particular role, because it is thought that, in parallel to inducing the transcription of expansins, auxin also activates plasma membrane proton pumps. The resulting cell wall acidification stimulates cell elongation, including expansins. This long-standing concept named “Acid Growth Theory” has been formulated in the 1970s. However, because of various discrepancies it has been controversial ever since, and 40 years later proof for its claimed universal applicability is still missing. Here we revisit this concept using state-of-the-art molecular genetic and micro-sensor tools. The main objective of the research is to comprehensively validate in a coherent experimental system to what degree the Acid Growth Theory can explain cell elongation in the root.

Poster | 4

The decision mechanism for Escherichia coli cell division under sporadic nutrients

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Typically microbes are growth in media with abundant carbon sources, but we know little about physiology, fitness, and the decision for division under naturally occurring conditions of sporadically-available nutrients. By subjecting starved E. coli to intermittent glucose exposures at increasing frequencies, we spanned glucose supply from non-growth sustaining levels to the threshold of the first proliferation (feedrate of ~0.2 mmol Glc/g DCW/hr). What does non-growing E. coli do with the consumed carbon? What are the molecular signals for proliferation?

To answer these questions, we leveraged a recently developed real-time metabolomics platform to monitor metabolite dynamics at a time-resolution of 10 seconds during pluses at different frequencies. During the non-growth regime, these metabolite dynamics suggest surprisingly that glucose rapidly sweeps through central metabolism and accumulates in biomass macromolecules such as proteins, DNA, RNA. This unsuspected and rapid accumulation of carbon in biomass, even in the absence of proliferation, was verified by 13C-labeling experiments and blocking macromolecular biosynthesis through antibiotics.

Increasing the pulse frequency beyond the growth threshold leads to cell growth after frequency-dependent lag times. Determining that the limitation of proliferation occurs with a specific protein, we narrowed to FtsZ, which forms the majority of the division stabilization ring. A simple dynamic FtsZ abundance model quantitatively relates lag time to the generation and depletion of FtsZ and was validated experimentally. The data, analysis, and approach provided here should expand study of microbial cell cycle in other time variant contexts.

Poster | 52

Biophysical and structural investigation of the Bik1 interaction network

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Microtubule plus-end tracking proteins (+TIPs) bind specifically to the growing plus-ends of microtubules and regulate the microtubule cytoskeleton. In the budding yeast S. cerevisiae, Bik1 (CLIP-170 homolog) and Bim1 (EB homolog) are two +TIPs that are important regulators of microtubule dynamics. Bik1 and Bim1 were reported to form a functional complex. In this work, we characterized in detail the interaction between Bik1 and Bim1 by isothermal titration calorimetry and identified the domains involved in Bik1-Bim1 complex formation. In addition, the region of Bik1 for Stu2 binding (homolog of the +TIP XMAP215/ch-TOG) has been identified. Furthermore, we found that the Bik1-Bim1 complex is capable of forming a ternary complex with EB binding SxIP or LxxPTPh peptide motifs present in many +TIPs as Kar9 (a protein involved in asymmetric cell division). We have solved the crystal structures of the Bim1 binding CAP-Gly domain of Bik1 alone and in complex with the Bik1 binding ETF motif of Bim1. These structures allowed us to design mutations in both Bik1 and Bim1, which perturb the interaction in vitro. By introducing these mutations in yeast cells, we were able to analyze the effects of the perturbations on Bik1 localization, Kar9 function, mitotic spindle positioning and microtubule dynamics.

Poster | 103

Multiscale, personalized modeling of blood-flow-related vessel-wall evolution

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The AneuX project investigates aneurysm evolution and rupture risk in a combined experimental-numerical approach. A framework and components for image-based, personalized multi-scale modeling of aneurysm blood flow and induced vessel wall remodelling have been realized, which has been applied to study the interplay between blood flow and cell structure adaptation, based on experimental data.

As part of this framework, an efficient, high-performance-computing-enabled fluid-structure-interaction (FSI) simulator is required. To decrease the computational complexity, a physically motivated two-level Schur-complement preconditioning approach was developed in combination with model-order-reduction of the surrounding vascular network.

The FSI simulator provides the hemodynamic wall-shear-stress to a cell vertex model (CVM), which simulates the endothelial cell shape adaptation under physiological and low flow conditions. It reproduces qualitatively endothelial cell elongation at specific aneurysm locations under the hypothesis that rearrangement of gamma-cytoplasmic actin, a component of the cytoskeletal network, is involved in the observed cell remodelling.

On the FSI side, current work focuses on supporting the complex, anisotropic and non-linear mechanical wall properties that are related to the evolving constituents such as collagen, muscle cells, elastin. On the CVM side, current work focus on hypothesis testing, extension to broader flow regimes, and model validation by experiments under aneurysm-like conditions.

Poster | 109

Investigating crowded metabolism: A molecular particle approach

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The intracellular environment is a crowded place. About 40% of its volume is occupied by macromolecules. When we observe a single metabolic reaction in this mixture, the presence of the other molecules has counteracting effects: On the one hand, the reduced volume increases the local enzymatic activity, and on the other hand, collisions with other molecules inhibit the diffusion of metabolites and enzymes. Even though it is known that crowding affects the kinetics of enzymatic reactions, little is known about its effects on cellular metabolism.

To investigate the effect of crowding on metabolic pathways we propose a molecular particle model based on Brownian Reaction Dynamics. Our model includes realistic crowding conditions to account for the diversity of macromolecules in the cell. We use this model to analyze the effects of crowding on enzymatic reactions and simple model pathways. Considering physiological relevant concentrations, saturations, and thermodynamic displacements we parametrize kinetic models and translate them into particle models with equivalent kinetics.

Our study shows that crowding affects enzyme kinetics under physiologically relevant conditions. We additionally present case studies on the consequences of crowding in metabolic pathways, revealing that further research is needed to understand the impact of crowding on metabolism.

Poster | 38

In vivo microtubule polymerization and dynamics requires polymerases in the budding yeast Saccharomyces cerevisiae

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The microtubule (MT) cytoskeleton in S. cerevisiae is polymerized out of two tubulin heterodimer isotypes, consisting out of one isoform of α-tubulin (Tub1 or Tub3) and β-tubulin (Tub2). While a wide variety of theoretical and computational models for in vitro MT dynamics exists, no current model considers the considerably lower tubulin concentrations in vivo. Here, we estimate the total and free concentrations of tubulin heterodimers in vivo. We contrast our estimates with experimentally determined tubulin concentrations in S. pombe and with experimentally determined critical concentrations for S. cerevisiae tubulin isoforms from literature, and find that tubulin concentrations in vivo are substantially lower than the concentrations that in vitro MTs require to grow. We extend previous in vitro theoretical and computational models with the MT-associated proteins Bim1, Bik1 and Stu2, and use individually measured in vitro data to quantitatively predict the in vivo polymerization of MTs given their interplay. Our predictions show that with the help of the MT polymerase Stu2 and plus-tip-targeting factors, MT dynamics can be enabled at much lower tubulin concentrations than for bare tubulin in vitro. The predictions of our in vivo model are consistent with experimental data on in vivo MT dynamics.

Poster | 54

Transparent in air and iridescent in water – structural analysis of a salamander egg sac

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The Hida salamander (Hynobius kimurae), a species endemic to Japan, lays an elongated egg sac and attaches it to the underside of stones in streams. Under water, the egg sac exhibits bright iridescence dominated by blue wavelengths, whereas it loses its iridescence and acquires an overall dull yellow hue when exposed to air. Both the physical mechanism underlying this iridescence and its possible biological function have remained unstudied. Here, we use FIB-SEM (focused ion beam scanning electron microscopy) to determine the 3D structure of the egg sac material with nanometer resolution and perform numerical simulations to compute the optical response of the egg sac from its actual geometry. Our analyses indicate that the Hynobius egg sac essentially consists in a 2D photonic crystal that can be efficiently modeled with a simple diffraction grating with a period of about 200 nm. Our model explains how the difference of refractive indices of water and air results in the presence or absence of egg sac's iridescence.

Single-Cell Biology

Chair:
Lucas Pelkmans
Institute of Molecular Life Sciences
University of Zurich

Speaker

The power of ONE: Immunology in the age of single-cell genomics

Ido Amit

Weizmann Institute of Science, Israel

Immune cell functional diversity is critical for the generation of the different regulator and effector responses required to safeguard the host against a broad range of threats such as pathogens and cancer, but also from attacking its own healthy cells and tissues. In multi cellular organisms, dedicated regulatory circuits control cell-type diversity and responses. The crosstalk and redundancies within these circuits and substantial cellular plasticity and heterogeneity pose a major research challenge. Over the past few years, we have developed a collection of innovative single-cell technologies, which provide unprecedented opportunities to draw a more accurate picture of the various cell types and underlying regulatory circuits, including basic mechanisms, transitions from normal to disease states and response to therapies. I will discuss some of our discoveries and how they change the current dogma in immune regulation as well novel technologies that combine single cell RNA-seq with CRISPR pooled screens and demonstrate the power of these approaches to probe and infer the wiring of mammalian circuits, fundamental to future engineering of immune cells towards desired responses, including immunotherapy.

Speaker

Reconstructing human development using single-cell transcriptomics

Barbara Treutlein

Max Planck Institute Leipzig, Germany

Recent advances in stem cell biology have made it possible to grow in vitro three-dimensional (3D) human organoids that model human development. We are using single-cell (sc) transcriptomics to reconstruct 3D organoid development and understand mechanisms underlying cell fate programming.

First, we use scRNA-seq to dissect and compare cell composition and lineage relationships in human cerebral organoids and fetal neocortex. We identify cells in the cerebral organoids that derived from regions resembling the fetal neocortex and find that these cells use gene expression programs remarkably similar to those of the fetal tissue. We then apply our approach to cerebral organoids derived from patients with brain malformations to identify molecular mechanisms underlying these neurodevelopmental disorders.

Second, we dissect 3D liver organoids generated by reconstituting hepatic, stromal, and endothelial cell interactions occurring during liver bud (LB) development. We use scRNA-seq to compare hepatocyte-like lineage progression from pluripotency in 2D culture and 3D LB organoids and find that organoid hepatoblasts diverge from the 2D lineage, and express epithelial migration signatures characteristic of organ budding. We benchmark 3D LB organoids against fetal and adult human liver, and find a striking correspondence between the LB organoid and fetal liver cells. We use network analysis to predict autocrine and paracrine signaling in LBs, and predict inter-lineage communication involved in LB vascularization and self-organization.

In summary, our molecular dissection of human organoid development provides an approach to systematically analyze and improve tissue engineering and illuminates previously inaccessible aspects of human organ development.

Speaker

From single-cell perturbation to subcellular analysis using fluidic force microscopy

Julia Vorholt

Institute of Microbiology, ETH Zurich, Switzerland

Single-cell biology provides unique insights into intracellular processes, cell-cell communication, and cell responses to exogenous stimuli, otherwise inaccessible to traditional bulk studies. While micromanipulation or cell sorting followed by cell lysis is already used for subsequent molecular examinations, approaches to directly extract the content of living cells remain a challenging but promising alternative to achieving non-destructive sampling and cell-context preservation. We developed a novel strategy to selectively perturb, isolate, or analyse single cells within physiological environments using fluidic force microscopy (FluidFM). The technology combines atomic force microscopy with microfluidics via microchanneled cantilevers with nano-sized apertures. Pressure control through the microchannel enables liquid release and aspiration with femtolitre resolution, whereas force spectroscopy allows for non-destructive insertion of the probe pyramidal tip inside a cell with real-time monitoring of cell indentation and membrane perforation. We demonstrate the quantitative extraction from single cells with spatiotemporal control. Molecular analyses of the withdrawn extracts permit the detection of enzyme activities, transcripts and metabolites. The established approaches provide unprecedented means to quantitatively inject or extract soluble molecules into/from single cells while preserving cell viability and physiological context.

Speaker

Long-term single-cell quantification: New tools for old questions

Timm Schroeder

D-BSSE, ETH Zurich, Basel, Switzerland

Despite intensive research, surprisingly many long-standing questions in stem cell research remain disputed. One major reason is the fact that we usually analyze only populations of cells - rather than individual cells – and at very few time points of an experiment – rather than continuously. We therefore develop imaging systems and software to image segment and track cells long-term, and quantify e.g. divisional history, position, interaction, and protein expression or activity of all individual cells over many generations. Dedicated software, machine learning and computational modeling enable data acquisition, curation and analysis. Custom-made microfluidics devices improve cell observation, dynamic manipulation and molecular analysis. The resulting continuous single-cell data is used for analyzing the dynamics, interplay and functions of signaling pathway and transcription factor networks in controlling hematopoietic, pluripotent, skeletal and neural stem cell fate decisions.

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Unraveling Cortical Development – Analyzing population and single-cell RNA-Seq data

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The brain is the most complex organ in the mammalian body and the mechanisms that regulate its development are poorly understood. During brain development, neural stem cells (NSCs) generate thousands of different neuronal subtypes that are organized in precise and functionally distinct layers of the cerebral cortex. This process is a prerequisite for normal brain functions.

To unravel these mechanisms, we study changes in the expression of transcription factors and signaling components in NSCs and progenitor populations (NeuroStemX). To this end, we use population and single-cell RNA-Seq of each population at daily intervals during mouse cortical development obtaining a data set containing more than 100 population samples and more than 1000 single cells. This enabled us to identify a set of novel genes that characterizes NSCs and progenitor cells at the population and single cell level at distinct stages of brain development. Using machine-learning methods, we identified a continuous differentiation path and, from this, determined different transcriptional states. Remarkably, we can show that the single cells follow a similar differentiation path to that predicted from transcriptional analysis at the population level. In addition, the single cells can be divided into subpopulations that emerge over time. In summary, our gene expression data of different cell types at the population and single-cell level for daily intervals during neurogenesis combined with the appropriate data analyses give an unprecedented insight into the complex process of stem cell patterning and fate decision-making in early brain development.

Short talk | 83

Dynamic single cell analysis of a cell fate decision system

Delphine Aymoz, Eric Durandau, **Serge Pelet**

UNIL-DMF, Lausanne, Switzerland

Cell fate decisions play a key role in developmental processes. To make choices, cells integrate multiple cues via signal transduction cascades. The mating response in budding yeast has often been considered as a cell fate decision system. In the presence of a potential mating partners, the cell can either continue to proliferate as a haploid cell or initiate a specific physiological program leading to the fusion of two partners. To study this process, we have developed fluorescent biosensors to quantify in single cells the dynamics of MAPK activity and protein expression. Surprisingly, when stimulating cells with exogenous pheromone, a lack of temporal correlation between MAPK activity and downstream transcriptional response can be observed. In cells that activate the MAPK within five minutes after stimulus, the induction of some promoters can be delayed by 30 minutes to an hour. We have studied the molecular mechanisms that control the timing of expression of mating dependent genes. In parallel, by analyzing hundreds of fusion events using automated image analysis, the physiological context of the expression of these genes has been investigated. This dataset allows to highlight the different steps taking place from the sensing of the two partners until their fusion.

Poster | 19

Fusing individual-based models with genome-scale metabolic networks - a novel approach for quantifying emergent microbial community spatiotemporal dynamics

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Metabolic capabilities of organisms govern their growth characteristics and their capability to adapt to changing environmental conditions. In natural systems, substrates can change dynamically and spatially with multiple species competing for resources. Genome-scale metabolic network models (GEMs) offer quantitative frameworks for consideration of the metabolism of organisms in the concourse. Community modeling has been used in studies to analyze multi-species consortia, however the high dimensionality of GEMs limits their use in complex systems especially for applications in spatially-explicit individual-based models (IBM). The use of IBM permits exploration of species interaction with their environment and neighbors within a prescribed physical domain. This study proposes to capitalize on recently developed algorithms, redGEM for the unbiased and systematic reduction of GEMs into reduced metabolic models (rGEMs) that retain compatibility with their parent GEMs. The reduced computational burden of rGEMs makes them scalable and makes their incorporation in IBM frameworks feasible. We formulated a hybrid model fusing an individual-based model (IBM) with advanced thermodynamics-based flux analysis (TFA) and reanalyzed a 3-member consortium comprised of E. coli, S. enterica and M. extorquens. While the IBM provides detailed description of the physical environment, motility characteristics of organisms, rGEMs and TFA provide a reduced description of the stoichiometric properties and bioenergetics constraints imposed on organisms, including intracellular and extracellular concentrations of metabolites at the local scale experienced by an individual. We report an approach that systematically merges stoichiometric models and individual-based models for study of interacting multispecies communities in physical spaces.

Poster | 71

Lung-on-a-chip microtechnologies for single-cell studies of host-pathogen interactions with M. tuberculosis

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A majority of host-M.tuberculosis encounters lead to latent infections in which the bacteria exist in a host-pathogen equilibrium, usually within granulomatous lesions in the lung. Although the structure and components of these lesions are well characterised, and the initial infection of macrophages by M. tuberculosis is well studied, the dynamic nature of this equilibrium, and the contribution of phenotypic heterogeneity within the bacterial population towards this process is less well understood.

We reconstitute, entirely in vitro, the murine alveolar interface within a lung-on-a-chip microfluidic device, building upon the previously reported human lung-on-a-chip system [1]. This system is then exposed to M. tuberculosis, and the progression of the infection is monitored through long-term time-lapse microscopy. This approach allows us to follow the chain of events from initial infection onwards at the single-cell level. Here, we report on the progress made in establishing the system and initial infection experiments carried out.

We will focus our investigations unresolved aspects about the innate immune response to the initial infection. As the system develops further, we will extend it to study the roles played by bacterial phenotypic variants in the process of granuloma formation. This will address challenging questions of immense significance for our understanding of latent TB and persistence during antibiotic therapy.

[1] D. Huh, B. D. Matthews, A. Mammoto, M. Montoya-Zavala, H. Y. Hsin, Donald E. Ingber, Reconstituting organ-level lung functions on a chip, Science 328, 1662-1668 (2010).

Poster | 95

Identification of genes that control the formation of membrane-less organelles

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Membrane-less organelles (MLOs) are subcellular compartments in eukaryotic cells that form through phase separation of proteins and RNAs from the surrounding milieu. MLO formation is driven by many factors, such as the concentration and multivalency of organelle components. However, the mechanisms by which cells control the assembly and dissolution of MLOs remain largely unknown. Altering protein multivalency by posttranslational modifications might be key to regulating MLO formation.

Here, we present the results of three parallel high-resolution image-based siRNA screens that enabled us to identify kinases and phosphatases that control the formation and dissolution of six major MLOs in human cells. As part of our automated image analysis pipelines we employed a pixel-based classifier to segment individual MLOs in more than 12 million single cells and extracted their phenotypic features. A self-organizing map algorithm was used to assign each cell to a distinct position in the dimensionality reduced feature space according to the phenotype of two multiplexed MLO markers each. Using this powerful single cell clustering approach we identified novel regulators of MLOs and show that perturbation of organelle homeostasis affects previously unlinked physiological processes. Our dataset will contribute to deciphering the regulation and biological functions of non membrane-bound organelles.

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High density lipoprotein-induced transcriptional response in primary human aortic endothelial cells

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Low blood levels of HDL-cholesterol are associated with coronary heart disease (CHD) and risk of diabetes mellitus type 2 (T2DM). Mechanisms mediating this association remain to be elucidated. As a potential mediator, we consider transcriptional mechanisms and specifically study the transcriptional response elicited by HDL particles for an endothelial cell model system. We evaluated the transcriptional response of primary human aortic endothelial cells (AEC) exposed to artificially reconstituted HDL (rHDL) by RNA sequencing after 6/10 hours. Differential expression analysis, GO term enrichment, and KEGG pathway enrichment analyses indicate a complex transcriptional response induced by rHDL. Ongoing work aims at achieving fine grained time- and single-cell resolved time series data of this transcriptional response. Specifically, we are performing droplet-based single-cell RNA-seq using the 10x Genomics Chromium device, achieving single-cell transcriptomes for up to 5,000 cells for each of the considered ten time points (0-36 h). This data will form the basis to derive dynamic models of the rHDL induced transcriptional response in endothelia. These models will potentially indicate most informative time points for subsequent single snapshot HDL perturbation experiments on the patient cohorts evaluated by the HDL-X consortium.

Poster | 66

Deciphering a prototypical MAPK signaling network using an optogenetic circuit

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Receptor tyrosine kinases (RTK) enable to convert extracellular INPUTs as growth factors into specific cellular OUTPUTs through the activation of dynamic signaling networks. Nowadays we have a good idea about network components, but we still miss crucial information about how these components are wired in a coherent signaling network. Our lab has recently brought new insights into the feedback and feed-forward structures regulating the ERK-MAPK network by delivering dynamical growth factor INPUTs with a microfluidic device and recording single cell ERK activation dynamics with an ERK biosensor[1]. In a next step, we propose to use a similar INPUT/OUTPUT approach together with system perturbations to identify the molecular players involved in the network regulation. To increase the experimental throughput, we propose to build a synthetic signaling circuit using an optogenetically activatable FGF receptor allowing to activate the MAPK network with light INPUTs instead of growth factors and a spectrally compatible ERK biosensor to record MAPK signaling OUTPUTs. Here, we provide an initial proof of concept of our experimental pipeline including the optoFGF receptor, a spectrally compatible ERK biosensor, and a computer vision platform for automatic image analysis at the single cell level.

[1] Ryu et al., Frequency modulation of ERK activation dynamics rewires cell fate, Molecular Systems Biology, 2015

Poster | 64

Inference of nonlinear mixed effect models from single-cell data using two-stage approaches

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Nonlinear mixed effect models (NLMEs) can be used to understand cell-to-cell variability of cellular dynamics from cell-specific variation of parameter values of a corresponding model of the underlying process. The principal methods to infer NLMEs are two-stage methods, where the population parameters are estimated from the individual parameters, and one-stage methods that use information on the population and individual level simultaneously. From a comparative study of the two approaches using a published dataset of single-cell trajectories and model, we conclude that when we have good quality and quantity of data as obtained in time-lapse imaging, the two-stage approaches can perform with the same accuracy as one-stage methods with significantly reduced computing times and increased simplicity in formulation. We then highlight the applicability of two-stage methods to a more complex model ---covering cell growth, endosome formation, protein dynamics and recycling--- to investigate the dynamics of Mup1 endocytosis in S. cerevisiae. From the NLME model, we identify the cellular processes contributing to the cell-to-cell variation.

Poster | 140

BioDataAnalysis CellAnalyzer uncovers complex cellular phenotypes of infection

Mario Emmenlauer

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Image-based assays are notoriously hard to analyze. Therefore, more often than not, the focus of analysis is on a robust but simple readout. However modern microscopy can resolve finest details and acquire numerous images, delivering a wealth of information. This information can reveal important aspects of the biological phenotypes under observation, which current analysis still fails to uncover. To empower the bio-medical researcher with no prior knowledge in image analysis machine leaning or data mining, we develop BioDataAnalysis CellAnalyzer, a highly automated analysis framework. Our software has been used to analyse the InfectX and TargetInfectX pathogen infection assays. We show how the use of improved image features provides new insight into the phenotypic space of Brucella and Bartonella infection into human cells.

Poster | 116

Understanding single cell - level MAPK activation dynamics for manipulation of neuronal stem cell self-renewal and differentiation fates

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Stem cell fate is controlled in vivo via the secretion of signaling molecules. Providing cultured stem cells with specific, developmentally relevant ligands is thus a promising approach for the generation of differentiated cells of a desired type for research or cell therapy. However, the efficiency of such protocols is often low, with many cells in the population escaping the desired fate. For example, adult neural stem cells from the mouse Dentate gyrus can be cultured as predominantly uncommitted, multipotent progenitor cells when EGF and FGF2 are provided in the medium or induced to differentiate into neurons and astrocytes when only FGF2 is provided. In both cases, however, the outcome is heterogeneous and ultimately determined at the single cell - level. Both EGF and FGF2 are prototypical activators of the ERK/MAPK – signaling pathway. We hypothesize that distinct temporal dynamics of ERK – pathway activation are responsible for the difference in cell fate and that these dynamic patterns are shaped by the MAPK network topology. Using quantitative imaging, we can study both the MAPK signaling and cell fate response of cultured Dentate gyrus stem cells to different growth factor types and concentrations at the single cell – level. Together with mathematical modelling, this data will give insight into how the MAPK network is wired to induce either self - renewal or differentiation fate in this cell type and might furthermore suggest ways to efficiently and homogeneously manipulate stem cell fate at the population level.

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Highly multiplexed and spatially resolved intracellular protein maps in thousands of single cells

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Obtaining reliable multiplexed protein measurements across spatial scales has enormous potential for biology and medicine. While various approaches achieve this at the tissue and cellular scale, their spatial resolution at the subcellular scale remains limiting. We here show the ability to obtain reproducible and highly sensitive 40-plex protein readouts from single cells at high-throughput, covering spatial scales from 9 mm2 to 25 nm2. It preserves the detailed morphology of intracellular organelles and cytoskeletal structures, allowing the simultaneous quantification of a wide range of molecular, subcellular, phenotypic, and cellular context readouts from the same sample, covering tens of thousands of single cells under various conditions. Such datasets uncover a richness of novel interactions across functional and spatial scales, and create high-resolution maps that capture the multivariate spatial distribution of proteins within an individual cell, enabling new types of analysis of single-cell responses to changes in cellular state, the microenvironment and drugs.

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Methods for quantitative single-cell time-lapse microscopy

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Quantitative single-cell time-lapse microscopy is crucial to advance our understanding of cellular behavior and its molecular control. However, such experiments produce huge amounts of imaging data whose quantitative analysis is hampered by a lack of user-friendly, generally applicable, fast and robust software tools for single-cell segmentation, tracking and quantification.

We therefore developed fastER (Hilsenbeck et al., Bioinformatics, 2017), a trainable tool for cell segmentation that is orders of magnitude faster than existing methods while producing state-of-the-art segmentation quality. It supports various cell types and image acquisition modalities, but is easy-to-use even for non-experts: it has no parameters and can be adapted to specific image sets by interactively labelling cells for training. In addition, we present The Tracking Tool (Hilsenbeck et al., Nature Biotechnology, 2016) a software pipeline for manual, computer-assisted single-cell tracking and quantification of cellular and molecular dynamics in long-term imaging data.

Both software tools are open-source and available for download at www.bsse.ETH Zurich.ch/csd.

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Investigation of localized loosening of the cell walls based on a microelectrode device

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Pollen tubes are tip-growing plant cells. Protons serve an important, regulatory role in the control of pollen tube growth. The generation of local guidance cues has been challenging when investigating the mechanisms of perception and processing of such directional triggers in pollen tubes. Here, we developed and characterized a microelectrode device to generate a local proton gradient and proton flux through water electrolysis. We confirmed that the cytoplasmic pH of pollen tubes varied with environmental pH change. Depending on the position of the pollen tube tip relative to the proton gradient, we observed alterations in the growth behavior, such as bursting at the tip, change in growth direction, or complete growth arrest. Bursting and growth arrest support the hypothesis that changes in the extracellular H$^+$ concentration may interfere with cell wall integrity and actin polymerization at the growing tip. A change in growth direction for some pollen tubes implies that they can perceive the local proton gradient and respond to it. We also showed that the growth rate is directly correlated with the extracellular pH in the tip region. Our microelectrode approach provides a simple method to generate protons and investigate their effect on plant cell growth.

Poster | 86

Towards systematic mapping of cell-cell communication events in the Arabidopsis root tip

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Abiotic stress conditions like drought or suboptimal phosphate levels can affect the root growth and architecture. We hypothesize that this relationship is mediated by alterations of peptide mediated cell-cell communication in the root. The RootBook project aims at assessing this hypothesis by developing technology to acquire and computationally process three dimensional, spatially resolved in situ sequencing maps of root tissues to identify cell-cell communication mechanisms. We focus on studying the model plant Arabidopsis thaliana. The envisioned in situ sequencing approach requires the definition of an explicit set of target transcripts. We defined a minimal set of genes associated peptide-mediated cell-cell-communication in the growing root. We acquired RNA sequencing data of root tip from wild type and peptide(-receptor) mutants and performed differential expression analysis to identify transcriptional targets associated with peptide mediated cell-cell communication. We found that knockout of peptide receptor HSL2 results in 110 potentially cell-cell-communication-related gene targets.

The next steps comprise translation of current prototype in situ sequencing assays for these targets. Finally, we will analyze these targets with dedicated spatial statistics and deep learning approaches to describe the cell-cell-communication induced relationships.

Poster | 11

A Short Linear Sequence Motif LxxPTPh Targets Diverse Proteins to Growing Microtubule Ends

Anil Kumar[1], Cristina Manatschal[1], Ankit Rai[2], Ilya Grigoriev[2], Andrea Prota[1], Rudolf Volkmer[3], Richard Kammerer[1], Anna Akhmanova[2], Michel O. Steinmetz[1]

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Microtubule plus-end tracking proteins (+TIPs) are involved in virtually all microtubule-based processes. End-binding (EB) proteins are considered master regulators of +TIP interaction networks, since they autonomously track growing microtubule ends and recruit a plethora of proteins to this location. Two major EB-interacting elements have been described: CAP-Gly domains and linear SxIP sequence motifs. Here, we identified LxxPTPh as a third EB-binding motif that enables major +TIPs to interact with EBs at microtubule ends. In contrast to EB-SxIP and EB-CAP-Gly, the EB-LxxPTPh binding mode does not depend on the C-terminal tail region of EB. Our study reveals that +TIPs developed additional strategies besides CAP-Gly and SxIP to target EBs at growing microtubule ends. They further provide a unique basis to discover novel +TIPs, and to dissect the role of key interaction nodes and their differential regulation for hierarchical +TIP network organization and function in eukaryotic organisms.

Poster | 75

Acoustic manipulation of single pollen grains

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The controlled three-dimensional manipulation of single cells opens new paths for plant research. We present a microfluidic device utilizing acoustically excited microbubbles to trap and rotationally manipulate Lilium longiflorum and Arabidopsis thaliana pollen grains. The biocompatible method enables the investigation of surface morphological features as well as the re-orientation of single cells for fluorescent analysis. Furthermore, three-dimensional access to the sample can be achieved through open-channel manipulation, granting all-around access to the plant cell.

Poster | 114

Characterizing Hydrophobic Adhesion of Epiphytic Bacteria with FluidFM

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ETH Zurich, Switzerland

There is increasing interest to manipulate and analyze single cells, e.g. to uncover cell-cell interactions, investigate single cell behavior in complex consortia, or quantify single-cell adhesion forces. Fluidic force microscopy (FluidFM) is a recently invented technology that addresses the demand for novel single-cell research, by combining atomic force microscopy with microchanneled cantilevers and microfluidics. The microchannels in the cantilever terminate in an aperture at the tip of the cantilever. Application of over- or underpressure allows controlled manipulation of liquids within the cantilever as well as controlled immobilization of micro-objects at the cantilevers tip.

Characterizing adhesion forces of single bacteria in their natural environment remains challenging, due to the small forces involved and demanding surface topographies. Combining the sensitive force-feedback of FluidFM with a modular system of functionalized colloids allows quantification of such, otherwise inaccessible, adhesion characteristics. To elucidate the mechanisms underlying the retention of epiphytic bacteria on waxy leaf surfaces, hydrophobic colloids are employed in this versatile system. Single-cell force spectroscopy (SCFS) measurements are performed with representatives of all bacterial phyla isolated from the Arabidopsis thaliana phyllosphere and highlight the differences in initial adhesion to hydrophobic substrates.

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Understand cellular heterogeneity in MAPK signalling by novel synthetic biosensor

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Cellular heterogeneity is always present in any population of cells. Due to cell-to-cell variability, individual cells can mount different responses upon activation by the same stimulus. To understand how individual cells process information and respond to perturbation, it is crucial to measure individual cell behaviors in a dynamics and quantitative manner and correlate it with the final cellular outcome.

Mitogen Activated Protein Kinases (MAPKs) transmit extracellular signals by generating a specific pattern of kinase activation dynamics, which can be decoded in a defined transcriptional response resulting in a specific phenotypic outcome. Using a synthetic biology approach, we generated fluorescent MAPK biosensors that undergo nuclear-to-cytoplasmic relocation upon phosphorylation named SKARS (Synthetic Kinase Activity Relocation Sensor). Using time-lapse microscopy, we can quantify the dynamics of kinase activation in real-time from more than thousand individual cells. In single cell clones, we found that the kinetics of the growth factor stimulated-ERK activation exhibit a large heterogeneity as function of their cell-cycle position. Moreover, ERK activity oscillated with low EGF doses, with the amplitudes and duration of pulses correlated with the stimulus. Overall, SKARS allows to quantify cellular heterogeneity and interpret how it is linked to biological function and cell fate decision.

Poster | 53

Identification of cell state transitions from single-cell expression data using a two-state model-based clustering algorithm

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The identification and characterization of different cell types within a heterogeneous population is an important step in the analysis of single-cell expression profiles. Standard unsupervised clustering strategies such as k-means and hierarchical clustering have previously been applied. However, the high variability in gene expression patterns and the high dimensionality of the data make the clustering problem not trivial. In this work, we present a clustering algorithm that explicitly takes into account the stochastic dynamics of gene transcriptional bursting using the two-state model, which estimates the rates that genes turn On/Off and the rate of transcription. We further employed the cell clustering outcome for three different tasks: (1) to define the developmental transitions that describe the cell differentiation progression, (2) to detect a subset of key genes representative of the transition signature, and (3) to infer the gene regulatory networks that govern the cell differentiation process. In these three tasks, we viewed each of the clusters as a “state” in the developmental trajectory. We demonstrated the efficacy of our algorithms on several published single-cell RT-qPCR and RNA-seq data sets.

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Single-cell protein dynamics around the cell cycle

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The cell cycle is an essential process that generates two identical cells with roughly the same content from only one mother cell. This process needs to be tightly regulated otherwise daughter cells will lack material essential for their upcoming growth. Using a dual fluorescent reporter composed of a fast (sfGFP) and slow (mOrange2) maturing proteins, we aimed at studying the protein dynamics (production and degradation) at the single-cell level around the cell cycle. We have generated a library of 50 mouse embryonic stem cell lines in which the timer is internally fused to endogenous proteins. By combining mathematical modelling, long-term live-cell imaging and single-cell tracking we were able to monitor the production and degradation rates of each clone in real-time at the single-cell level. We discovered that, while most proteins accumulate linearly during interphase, dynamics of protein synthesis and degradation around mitosis are more heterogeneous. In fact, proteins dynamics around mitosis could be grouped in three categories where 10 % increase their degradation and decrease their production, 50 % only decrease their production and 40% either keep constant production and degradation or decrease their degradation. Together, our results revealed an unanticipated diversity of protein dynamics around mitosis.

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Quantitative live-cell analysis of transcriptional memory in dividing mammalian cells

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Gene expression in embryonic stem (ES) cells is both highly dynamic and heterogeneous within the same culture, which means that responses to subsequent environmental cues can be divergent. Fluctuations in single-cell gene expression are caused by randomness in biochemical reactions involving low numbers of molecules (intrinsic noise) and cell-to-cell variability in macroscopic states (extrinsic noise). Understanding fluctuations in gene expression is important because they can have a profound phenotypic impact (such as providing a heterogeneous response to a sudden stress), and may be buffered against or exploited across a range of systems. Here we develop novel computational techniques to analyse live imaging of transcriptional reporters in single, proliferating ES cells. We combine live imaging and model-based inference to explicitly quantify the similarity in transcriptional dynamics between sister cells after division, and reveal the degree to which transcriptional dynamics are inherited and propagated in ES cultures.

Poster | 28

Unraveling tumor heterogeneity with deep learning and mass cytometry data

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Understanding how tumor heterogeneity affects clinical outcomes has become a cornerstone for developing effective treatments. Mass cytometry (CyTOF) enables the simultaneous quantification of ~50 proteins in thousands of cells, offering unprecedented resolution on the tumor ecosystem. To date, a number of computational methods to analyze CyTOF data exist, however the complex and highly-non linear nature of the relationships between the measured markers is still not properly addressed.

We present ongoing work to analyze, correct and characterize CyTOF data. We first apply our newly-developed tool, CellCycleTRACER, to account for cell-cycle and cell volume confounding effects. Next, we explore the use of deep learning approaches to reduce the dimensionality of CyTOF data and identify clinically meaningful patterns. Specifically, we employ denoising and variational autoencoders to minimize the effect of noise, enforce robustness despite partially destroyed inputs and missing data, and generate compressed representations that capture the main relationships between markers. We also propose a modified network architecture to simultaneously identify cell subpopulations and predict their disease associations. We test our approach on CyTOF data from (i) a cohort of breast cancer patients and (ii) a mouse PDX model before and after breast cancer metastasis. Our results indicate that mapping cell subpopulations in the learned reduced-dimensional space together with clinical information can uncover relationships between populations and/or tumors that could otherwise go unnoticed, while simultaneously elucidating metastasis-specific cell subpopulations.

Poster | 97

Topographic analysis of the tumor ecosystem using imaging mass cytometry

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Single-cell, spatially resolved 'omics analysis of tissues is poised to transform biomedical research and clinical practice. Next-generation imaging methods like highly multiplexed Imaging Mass Cytometry provide unique insights into the complex tumor ecosystem and architecture in single cell resolution. These data sets allow the analysis of topographic features and cell compositions simultaneously. We have developed a computational multiplexed image cytometry analysis toolbox (miCAT) to enable the interactive, quantitative, and comprehensive exploration of phenotypes of individual cells, cell-to-cell interactions, microenvironment, and morphological structures within intact tissues. miCAT will be useful in all areas of tissue-based research. We highlight the unique abilities of miCAT by analysis of highly multiplexed mass cytometry images of human breast cancer tissues.

*Authors contributed equally to this work

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Towards understanding the transcriptional network directing lipid droplet biogenesis

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While lipid droplets are omnipresent in most cells where they serve as the primary storage site of neutral lipids, the number and nature of these organelles varies greatly, both over time and between cell types. Although several stimuli have been identified to induce accumulation of lipid droplets, including activation of the Wnt signaling pathway, the proximal transcriptional regulators remain unclear. Therefore, we initiated a multipronged approach to identify the transcription factors directing the biogenesis of lipid droplets, including RNAseq and an in silico examination of the promotor region of lipid droplet related genes. Together, this examination of the transcriptional regulation lead to identification of several candidate factors that may serve as part of the “master” regulatory network controlling lipid droplet biogenesis and include members of the C/EBP family (known regulators of adipogenesis), FHL2 and CBP/P300 elements of the Wnt signaling pathway, and the TFAP2 family of transcription factors. We found siRNAs to several of these diminished the accumulation of LDs in response to Wnt stimulation while overexpression was sufficient to induce LD accumulation in cells, confirming the role of this transcriptional network in directing LD biogenesis.

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Quantitative analysis of mouse ESCs phenotypes using single-cell live imaging

Stavroula Skylaki[1], Denis Shapiro[2], Hartland Jackson[2], Stefanie Engler[2], Andreas Reimann[1], Simon Hastreiter[1], Dirk Loeffler[1], Bernd Bodenmiller[2], Timm Schroeder[1]

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Embryonic stem cells (ESCs) have the unique abilities to self-renew and differentiate to the three primary germ layers. Even though ESCs consist of a genetically homogeneous cell population, a number of studies have reported heterogeneity in ESCs cultures as a result of fluctuations in the expression of key regulators responsible for maintaining the ESC identity. Moreover, even under standard self-renewing conditions, ESCs display a range of different morphologies that are rarely reported in literature, mainly due to technical challenges. Here we combine long-term single-cell live imaging of high spatiotemporal resolution with automated computational approaches to enable a comprehensive quantitative analysis of the molecular and phenotypic dynamics of mouse ESCs. In addition to simultaneous live single-cell quantification of protein levels of pluripotency transcription factors and/or activity of signaling pathways, we quantify features related to morphology (size, texture, orientation etc.) and behavior (motion, speed, etc.). Furthermore, we combine continuous single cell live imaging data with high-dimensional snapshot data from imaging mass cytometry (IMC) to obtain an IMC-based representation of the cell states landscape in pluripotency and lineage specification. To integrate this unique combination of single-cell data to investigate the molecular basis of ESCs fate control, we develop the required novel computational tools and models.

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Input-output relationships underlying transcriptional dynamics

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Environmental stimuli elicit intracellular responses through signaling pathways, which converge on transcriptional activation or repression of target genes. Recent single-cell analysis studies have reported the stochastic nature of transcription, in particular, the phenomenon of transcriptional bursting. In this work, we aim to understand the quantitative relationship between upstream factors and transcriptional kinetics by developing an experimental system to temporally monitor, simultaneously, inputs (transcription factors) and outputs (target gene expression) in mammalian cells. In order to link the upstream transcription factor (TF) expression profile to its target gene activity, we established two Tet-On inducible stable cell lines each expressing a fusion protein of a luminescence (Nanoluc) reporter to either SMAD4 or SMAD2, the two main transcription factors downstream of the TGF- signaling pathway. These cell lines that also contain a short-lived firefly luciferase reporter for the expression of the target endogenous ctgf gene allowed us to quantitatively link nuclear accumulation of TFs upon TGF- stimulation to the target gene expression in real-time single cell measurements. Time-lapse luminescence microscopy and its image analysis with the custom developed CAST platform indeed showed single cell dynamics of translocation of SMADs into the nucleus upon TGF- stimulation followed by ctgf gene response. Combined with mathematical analysis, our experimental single-cell data aims at decoding the underlying regulatory effect of translocation dynamics on the target gene expression.

Poster | 20

A kinetic model of the lipid network in yeast

Sophia Tsouka, Georgios Savoglidis, Vassily Hatzimanikatis
EPF Lausanne, Switzerland

Lipids play a very important role in cell structure and function, as well as in the physiopathology of many diseases. Maintenance of the lipid profiles should be tightly regulated as it is very important for preserving membrane permeability, cell integrity and several other functions. Large-scale kinetic models of metabolic networks are essential in order to accurately capture and predict such behaviors of cellular systems when subject to perturbations. We have thus developed a detailed model of the lipid metabolism for the yeast S. cerevisiae, in order to identify how the stoichiometric and kinetic coupling determines lipid homeostasis and its regulation. The model encompasses 308 reactions and 212 unique metabolites, and includes the following subsystems: glycolysis, fatty acid biosynthesis and elongation, biosynthesis of phospholipids, sphingolipids, cardiolipin and sterols, triacylglycerides decomposition and the mevalonate pathway. We curated this model using thermodynamic data as well as lipidomic measurements and we used the Optimization and Risk Analysis of Complex Living Entities (ORACLE) framework to generate populations of parametrized kinetic models that are consistent with the given physiology, while satisfying the stoichiometric and thermodynamic constraints. We used these models to identify parameters (i.e. enzyme activities) that determine lipid distribution and homeostasis.

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Mechanical properties of the cell wall control cellular morphogenesis

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It is becoming increasingly clear that the mechanical properties of cells and tissues play a key role in cell fate determination, pattern formation and tissue homeostasis. Growth and morphogenesis in plants are to a large extent determined by the mechanical properties of the cell wall. Using fast-growing pollen tubes as a model system allows us to to measure the mechanical properties of individual cells, avoiding effects of surrounding tissue. The tip-growing nature of pollen tubes allows comparative measurements between highly dynamic and inert regions of the cell wall in the same cell.
To understand how the biochemical composition and physiological parameters affect the mechanical properties of the cell wall, we developed a systems biology approach combining cellular force microscopy (CFM) and simulation techniques (finite element method, FEM) to extract such properties and derive quantitative models of cellular morphogenesis. We investigated changes in mechanical properties and growth parameters of Arabidopsis mutants with an altered biochemical composition of the cell wall, affecting its major load-bearing components. Quantitative measurements and simulations allowed us to investigate the interplay between mechanical and biochemical properties of the cell wall. The power of our systems approach is revealed by its ability to predict cellular growth and morphogenesis of wild-type and mutant pollen tubes.

Poster | 94

Control of stochastic promoter choice in the protocadherin cluster

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Biozentrum, University of Basel, Switzerland

Genes in the protocadherin (Pcdh) cluster are arranged in a tandem array and each gene is expressed in a stochastic fashion in neurons. The cluster is regulated by an interplay of long-range interaction between promoters and enhancer and epigenetic modifications. Since the effect of this regulation on the stochastic expression remains unknown, we studied the interdependence among stochastically expressed genes. We show that the expression of genes in the Pcdh cluster is independent, when embryonic stem cells differentiate into neurons. A synthetic transcriptional activator targeted to a specific gene at its native locus activates specifically the target gene in ES cells. On the other hand, the same activator behaves like an enhancer at the progenitor state as the entire cluster is activated, with an overall positive correlation of the stochastically expressed genes in the cluster. Hypomethylation of promoters upstream of the target gene coincides with this enhancer-like effect. In addition, binding of CTCF, which mediates loop formation between the promoters and the enhancer, correlates positively with expression of individual genes. These results suggest that there is a switch in the transcriptional regulatory logic during the differentiation process, which modulates the spatial effect of transcriptional regulation according to the differentiation state.

Poster | 69

Molecular Signaling Fingerprinting of Human Hematopoietic Stem Cell (HSC) Fate

Weiija Wang, Timm Schroeder
D-BSSE, ETH Zurich, Basel, Switzerland

Despite decades of research on HSCs, little is known about the molecular mechanisms by which HSCs integrate their environmental signals and determine cell fate. It has become clear that the intracellular “signal processing” network is highly interconnected and that the network’s state, rather than isolated pathways dictates cellular outcome. Therefore, systems-level approaches are required to obtain a comprehensive understanding of the molecular control of HSC fate. Additionally, the lack of direct measurement of both intracellular signaling activity and functional outcome of the same cell has limited the development of models that can predict cellular responses of a heterogeneous population such as HSCs. To overcome these limitations, interdisciplinary methods including live cell imaging, fluorescent biosensors, microfluidics, and computational models are used to directly connect intracellular signaling dynamics with cell fate outputs in human HSCs at the single cell level. Proof-of-principle experiments have demonstrated the feasibility of introducing translocation-based biosensors into human umbilical cord blood-derived CD34+ cells to enable the continuous and quantitative measurement of the signaling pathway (e.g., phosphoinositide 3-kinase (PI3K)) activation in single, live cells. These single-cell signaling dynamics data, together with data-driven models will be used to identify key signaling nodes that control the cellular outcomes in human HSCs.

Poster | 46

Transcriptional memory in the HOG pathway

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Sudden exposure to stressful conditions requires rapid and functional response of cells in order to survive and adapt to this new environment. In S.cerevisiae changes in osmolarity are sensed by the High Osmolarity Glycerol (HOG) pathway. Signal transduction leads to the activation of the key effector protein Hog1, a Mitogen Activated Protein Kinase (MAPK). Upon activation, Hog1 phosphorylates substrates in the cytoplasm and relocates to the cell nucleus to induce gene expression. Most osmostress responsive genes, like STL1, are repressed in basal conditions due to close chromatin conformation. Activated Hog1 is responsible for the recruitment of chromatin remodelling complexes and the transcriptional machinery to the locus. Because of the transient activation of the MAPK and the simultaneous recruitment of negative regulators, active transcription is ephemeral. Using a live single-cell reporter of promoter transcriptional activation (PP7 system), we monitored the activation of the STL1 promoter under single or consecutive stresses. Interestingly, priming of the cells with mild stimuli leads to a refractory period of up to an hour where this locus cannot be reactivated. Using reverse genetics and single-cell data analysis, we aim at describing the molecular mechanism behind this locus inhbition. Whether this negative memory is a side effect of efficient transcription deactivation or an adaptive mechanism to increase the cell fitness is to be investigated.

Systems Genomics

Chair:
Bart Deplancke
Laboratory of Systems Biology and Genetics
EPF Lausanne

Speaker

Personalized medicine approaches based on gut microbiota

Eran Segal
Weizmann Institute of Science, Israel

Elevated blood glucose levels are rapidly increasing in the general population, resulting in a sharp incline in the prevalence of pre-diabetes and impaired glucose tolerance, and eventual development of type II diabetes mellitus. Dietary intake is considered a central determinant of glucose levels, with high post-meal glucose levels affecting weight gain, obesity, hunger, energy dips, and being associated with increased risk of cardiovascular disease, cancer, and overall mortality. However, despite their importance, existing dietary methods for controlling post-meal glucose levels have limited efficacy.

By continuously monitoring week-long glucose levels in over 1,000 people, we found high variability in the response of different people to identical meals, suggesting that generic population-wide dietary recommendations have limited utility and are ineffective in achieving proper glycemic control. We devised a machine-learning algorithm that integrates blood parameters, dietary habits, anthropometrics, physical activity, and gut microbiota measured in this cohort and showed that it accurately predicts personalized postprandial glucose responses to real-life meals. Moreover, a blinded randomized controlled dietary intervention based on this algorithm resulted in significantly lower postprandial responses in a cohort of pre-diabetics and consistent alterations to gut microbiota configuration. These results suggest that personalized diets may successfully modify elevated postprandial blood glucose and its metabolic consequences.

Finally, I will also present our studies of the mechanisms driving recurrent post-dieting obesity in which we identified an intestinal microbiome signature that persists after successful dieting of obese mice. This microbiome signature contributes to faster weight regain and metabolic aberrations upon re-exposure to obesity-promoting conditions and transmits the accelerated weight regain phenotype upon inter-animal transfer. Notably, a microbiome-based machine-learning algorithm enabled personalized prediction of the extent of post-dieting weight regain.

We further find that the microbiome contributes to diminished post-dieting flavonoid levels and reduced energy expenditure, and demonstrate that flavonoid- based 'post-biotic' intervention ameliorates excessive secondary weight gain. These results thus highlight a possible microbiome contribution to accelerated post-dieting weight regain, and suggest that microbiome-targeting approaches may help to diagnose and treat this common disorder.

Speaker

Survey of coding variation in human transcription factors reveals prevalent DNA binding changes

Martha Bulyk

Harvard Medical School, United States

Sequencing of exomes and genomes has revealed abundant genetic variation affecting the coding sequences of human transcription factors (TFs), but the consequences of such variation remain largely unexplored. We developed a computational, structure-based approach to evaluate TF variants for their impact on DNA-binding activity and used universal protein binding microarrays (PBM) to assay sequence-specific DNA-binding activity across 41 reference and 117 variant alleles found in individuals of diverse ancestries and families with Mendelian diseases. We found 77 variants in 28 genes that affect DNA-binding affinity or specificity and identified thousands of rare alleles likely to alter the DNA-binding activity of human sequence-specific TFs. Altered sequence preferences correlated with changes in genomic TF occupancy (ChIP-Seq peaks) and gene expression of the associated target genes. Our results suggest that most individuals have unique repertoires of TF DNA-binding activities, which may contribute to phenotypic variation.

Speaker

Contribution of non-coding DNA to complex traits and cancer

Emmanouil Dermitzakis

University of Geneva Medical School and SIB Swiss Institute of Bioinformatics, Switzerland

Molecular phenotypes inform us about genetic and environmental effects on cellular and tissue state. The elucidation of the genetic basis of gene expression and other cellular phenotypes is highly informative for the impact of genetic variants in the cell and the subsequent consequences in the organism. In this talk I will discuss recent advances in key areas of the analysis of the genomics of gene expression, chromatin and cellular phenotypes in human populations and multiple tissues from the GTEx consortium and how this assists in the interpretation of regulatory networks and human disease variants. I will also discuss how these recent advances are informing us about the impact of regulatory variation in cancer.

Speaker

Cracking the genetic basis of human longevity

Zoltan Kutalik

University of Lausanne, Switzerland

The enormous variations in human lifespan are in part due to a myriad of sequence variants, only a few of which have been revealed to date. We developed a Mendelian randomization-based (MR) method combining 12 disease-related GWA studies to derive disease-informed longevity priors for all SNPs genome-wide. Our Bayesian association scan, informed by these priors, for parental age of death in the UK Biobank study (n=116,279) revealed 16 independent SNPs with significant Bayes factor at a 5% false discovery rate (FDR), 12 of which are novel and 11 of them replicate (5% FDR) in five independent longevity studies combined. While many of them have pleiotropic effects, three have not been associated with any human trait to date. Interestingly, all but three of them have life-shortening alleles that are depleted in older Biobank participants. Further causal inference analysis revealed that lower expression levels of *RBM6, SULT1A1* and *CHRNA5* in the brain might be causally implicated in longevity. Our follow-up animal experiment showed, consistently with the human results, that lower mRNA level of *RBM6* in prefrontal cortex at 72 days of age was a strong predictor of shorter lifespan in the LXS mouse lines. Finally, genome-wide analysis revealed significant enrichment for the lipoprotein metabolism pathway and largely shared genetics with extreme longevity.

Short talk | 7

Isoform-specific localisation of DNMT3A regulates DNA methylation turnover at bivalent CpG islands

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DNA methylation is a prevalent epigenetic modification involved in transcriptional repression and essential for mammalian development. Although the genomic distribution of this mark has been profiled at unprecedented detail, the mechanisms responsible for its correct deposition, as well as the cause for its aberrant localisation in cancers, have not been fully elucidated.

We have previously identified the specific genomic localisation and activity of DNA methyltransferases in mouse embryonic stem and neuronal cells, and have revealed a regulatory feedback loop that reinforces DNA methylation targeting to transcribed gene bodies (Baubec et al., Nature 2015). In recent unpublished work we report a division of labor between two tissue-specific DNMT3A isoforms. We show that the longer isoform DNMT3A1 preferentially localises to the borders of CpG islands, whereas the shorter isoform DNMT3A2 is globally distributed throughout the genome. DNMT3A1 localisation further coincides with elevated hydroxymethylcytosine deposition, and through combining genetic deletion and rescue experiments with genome-wide studies we demonstrate that isoform-specific recruitment is required for rapid turnover of DNA methylation at regulatory regions.

We will present the isoform-regulated mechanism responsible for DNA methylation homeostasis at CpG island borders in more detail, and propose that this mechanism is required to define cell type-specific transitions between methylated and unmethylated domains - with further implications on Polycomb gene regulation. The isoform-specific activity of DNMT3A extends our current understanding on how the writers of DNA methylation target specific genomic regions and cooperate to shape the epigenetic landscape of mammalian cells.

Systems analysis reveals high genetic and antigen-driven predetermination of antibody repertoire diversity and development

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Antibody repertoires change across multiple B-cell developmental stages and in response to antigen exposure. Although repertoire diversity is crucial for broad protective immune responses, vaccination success and the development of novel therapies, we still lack fundamental understanding of the extent to which this diversity is predetermined or stochastic. Therefore, we implemented a systems immunology framework for quantifying repertoire predetermination on three distinct levels in mice: (i) B-cell development – focus on the key B-cell stages pre-B cell, naïve B cell and memory plasma cell, (ii) antigen challenge – three structurally distinct proteins and (iii) four major antibody repertoire components – V-gene usage, clonal expansion, clonal diversity, repertoire size, extracted from high coverage antibody repertoire sequencing data – 400 million full-length antibody variable heavy chain sequences. We discovered that the humoral immune system is more predictable than previously thought by revealing high genetic (maximum 99%) and antigen-driven (maximum 40%) repertoire predetermination across all three B-cell developmental stages and independent of mouse strain. These results have implications for the prediction and manipulation on the humoral immune system.

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Unraveling the molecular basis of local sequence-independent, regulatory variation in humans

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Most common disease associated genetic variants are located outside of gene-coding regions. This makes the task of identifying their function remarkably complicated. Only few studies have been able to pinpoint the mechanism of non-coding variants contribution to setting up complex traits or disease phenotype. One of the inherent reasons is that only minority of variable inter-individual transcription factor (TF) binding events can be explained by a local motif disruption. A work in our group has lately demonstrated that a single variant can determine coordinated TF binding and histones modification changes along a span genomic regions over 100kb. Such regions, termed variable chromatin modules (VCMs), provide a rationale for local sequence independent TF binding variation, emphasizing the importance of short and long range TF interactions to regulate activity of a genomic locus.

Here we address the molecular mechanisms of VCM action and provide experimental evidence that a single TF-DNA interaction may impact the activity of an extended genomic region. We are also exploring the plasticity of VCMs in the context of an evolving transcriptional program during human adipogenesis. Our results might disclose molecular mechanisms of modular genome organisation and contribute to the interpretability of non-coding GWAS variants, so far largely uncharacterized.

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System-Based Identification of Genetic and Environmental Regulators of Virulence in Mycobacterium tuberculosis

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Tuberculosis is caused by Mycobacterium tuberculosis (Mtb) and claims 1.8 million lives annually. To date, Mtb research efforts have largely relied on the lab-adapted model strain, H37Rv, and focused on its transcriptional responses. However, clinical isolates of Mtb reveal diverse phenotypic features that are thought to be most directly determined by the state of the proteome. Here, we aim to identify genotype – proteotype relationships resulting in biomolecular networks driving various phenotypes.

We analyzed the proteome of 70 fully sequenced clinical isolates of Mtb grown under normal and nitric oxide stress replicating the physiological environment that the bacilli experience following uptake by macrophages. Illumina NGS and SWATH-MS have paved the way to profile the genome and proteome of the strains respectively.

The dataset revealed ~600 significant changes (out of ~2600) at the proteome level between lineage 1 and 2 strains while their genomic distance is ~1200 SNPs. We elucidated that DosR and IdeR regulon were significantly upregulated in lineage 2 strains whereas the essential genes remained unchanged. The higher basal expression of DosR, most likely caused through Rv1985c by pknH, explains why lineage 2 frequently encompasses drug resistant strains in comparison to other lineages. Our model indicates transcription factors Rv3133c/DosR, Rv0081 and Rv0576 as playing major role in orchestrating the transcriptional network of lineage 2 in respect to lineage 1 strains. We have shown that how genomic differences between the clinical isolates determine the state of the proteome using QTL analysis.

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Mitochondrial variation and its impact on metabolic phenotypes in Drosophila melanogaster

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Variation in metabolic phenotypes is driven by genetic and environmental factors. It has recently become apparent that not only the nuclear but also the mitochondrial genome contributes to metabolic traits. The extent of mitochondrial genetic variation and how it interacts with environmental factors such as diet is however still poorly understood. To address this, we sequenced the mitochondrial genomes of 180 Drosophila Genetic Reference Panel (DGRP) lines to obtain a high-resolution chart of mitochondrial genomic variation. We uncovered 223 variants of which 49 novel SNPs and 22 indels. Seven of these variants introduce frameshifts affecting core mitochondrial respiratory proteins (i.e. ND1, ND2, COX1). We are currently validating these mutations via systematically screening for mitochondrial supercomplex formation across the DGRP using BN-PAGE. Additionally, we are studying the effect of mitochondrial variants on the metabolic response to a high fat diet. This diet, characterized by increased triglyceride levels and expression of insulin-related genes, results in a strong reduction in lifespan ranging from 18% up to 67% in >100 DGRP lines. Based on these findings, we are currently identifying genetic mito-nuclear interactions that contribute to this phenotype. Our study demonstrates the benefits of integrating mitochondrial genomic variation in GWAS analyses investigating metabolic phenotypes.

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A multicenter, multiyear, study of the genetic basis of longevity in genetically diverse mice

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Longevity is a complex trait that is mediated by a combination of genetic and environmental factors (e.g. diet, drug/toxin exposure, physical activity). The relative contribution of these factors remains elusive. To dissect and expose key gene variants and mechanisms that modulate longevity, we have begun to genotype a large intercross of mice from the NIA Interventional Testing Program (UM-Het3; a 4-way F2 of BALB/cByJxC57BL/6J-F1s to C3H/HeJxDBA2J-F1s). This intercross segregates for ~7 million variants. Cases have been raised in three sites (Michigan, Maine, and Texas), and exposed systematically to a wide range of dietary and drug interventions (e.g., aspirin, rapamycin, resveratrol, etc; see https://www.nia.nih.gov/research/dab/interventions-testing-program-itp/papers-nia-interventions-testing-program).

As a result the cohort is ideal for the analysis of gene-by-environment and particular gene-by-drug interactions that modulate lifespan. At present, we have mainly genotyped control mice from all three sites at no fewer than 200 SNP markers across all chromosomes. Preliminary analyses based on 2400 cases reveal that the genetic determinants of longevity as well as weight gain are sex-specific. Additional samples are now providing us with a powerful panel to study the genetics of longevity in relation to sex, treatment, environment, and body weight status.

Poster | 105

Image-based profiling of single cell CRISPR-Cas9 gene perturbation phenotypes.

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CRISPR-Cas9 has emerged as a powerful tool for genome editing in mammalian cells and has been applied in functional genomic screening. The large-scale CRISPR-Cas9 screens performed to date have used a pooled screening format, precluding image-based phenotyping of individual cells. We set out to develop methods for arrayed, image-based CRISPR-Cas9 screening. We addressed three key issues. First, we characterized CRISPR-Cas9 mediated gene perturbations in human tissue culture cells. We evaluated the gene perturbation phenotype in thousands of single cells using automated microscopy. Second, we developed a pipeline for high throughput generation of CRISPR-Cas9 targeting plasmids to construct an arrayed screening library of approximately 2200 plasmids targeting ubiquitin ligases, kinases and phosphatases. Third, we developed a statistical approach for multivariate 'hit' identification and the phenotypic characterization of genetic perturbations using multivariate single cell measurements.

We applied this library in an image-based screen and identified several classes of genes affect cell shape and the subcellular localization of a marker of the nuclear pore complex. Our framework is scalable to the genome level and will serve as a template for future image-based CRISPR-Cas9 gene perturbation screens.

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Genome-wide impact of DNA methylation on transcription factor binding

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Chromatin has the potential to restrict accessibility of transcription factor (TF) binding sites; however, in which contexts chromatin states are instructive for TF binding remains mainly unknown. Here we systematically explore the contribution of DNA methylation to constrained TF binding in vivo.

The absence of DNA methylation has little impact on cell survival or global TF binding in mouse stem cells (Domcke, Bardet et al. Nature 2015). To test whether more TF binding events are affected by DNA methylation in differentiated cells, where it is essential, we generated neuronal cells without DNA methylation (DNMT TKO neurons). These cells survive for several days and remarkably resemble the WT in morphology and gene expression. Although we identify a fraction of TF motifs that are only bound in the absence of DNA methylation, overall chromatin accessibility is surprisingly similar. In contrast, specific long terminal repeat (LTR) retrotransposons, the intracisternal A particles (IAPs), are derepressed by several orders of magnitude in TKO neurons. Sequence comparison of activated and silent elements of the same IAP subtype reveals that the presence and strength of a specific TF motif within the LTR is highly predictive of the level of activation in TKO neurons. We suggest that DNA methylation is required to block binding of TFs at this motif in neurons and thus prevents the potentially lethal derepression of transposable elements.

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Genome-wide siRNA/miRNA screens reveal regulatory network behind ITGB1-mediated Bartonella henselae infection

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Entry routes of human pathogens into host cells are of major interest in infection biology. In the frame of InfectX, we explored the human infectome of several bacteria and viruses in HeLa cells. Standardised microscopy-based siRNA/miRNA-screens were elaborated to allow for enhanced comparability among pathogens. We applied this workflow to the Gram-negative zoonotic bacterium Bartonella henselae. Its infection phenotype is characterised by invasomes, internalised bacterial clusters tightly surrounded by actin. Our screens confirmed the importance of ITGB1-TLN1 signalling and identified novel factors relevant for generation of invasomes. In particular, the ITGB1-binding protein FERMT2 and miR-29 influence invasome numbers. We demonstrate that miR-29 regulates FERMT2 transcript levels by direct binding to its 3'-UTR. FERMT2 together with DNMT3 repress miR-200 expression. A lack of those proteins or increased miR-200 levels hamper invasome formation. In line with ITGB1 and FERMT2 contributing to cell-substratum contacts, elevated levels of miR-29 and miR-200 lead to altered focal adhesion morphology.

It is currently under investigation at what stage of the infection these transcripts are essential. A comparison to other InfectX pathogens will reveal if they exclusively influence induction of invasomes by B. henselae or if also other pathogens dependent on ITGB1 require these factors for successful infection.

Poster | 23

Analysis of Ski as a regulator of neural stem cell transcriptome dynamics

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During cortical development many genes and signaling pathways are active but their functions and interconnections are poorly understood. Taking advantage of in vivo transgenic labeling, we analyzed gene expression of neural stem cells (Hes5::GFP; Ski-/-) and committed neuronal progenitors (Tbr2::GFP; Ski-/-) from wild type and embryos lacking Ski, a pivotal signaling and transcriptional regulator involved in cortical development and cancer. Patients with 1p36 syndrome have a deletion of the Ski gene and they are affected by microcephaly, cranial malformations and intellectual disabilities.

It is unclear how Ski functions in brain development, we now have a unique dataset that includes pathways affected by loss of Ski in developing brain. We found that Ski-deficient NSCs are locked in a prolonged neurogenic phase and fail to switch to a gliogenic fate. Performing in utero electroporation experiments knocking-down or over expressing Ski at different stages of development we are evaluating the cell autonomous effects and the molecular function of Ski in neural stem cells.

Moreover, ISMARA (Integrated System for Motif Activity Response Analysis) allowed us to identify the transcription factors that show divergent activity profiles in Ski Wt and Ski KO neural stem and committed progenitor cells.

Poster | 13

Patterns of ribosomal protein expression specify normal and malignant human cells

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Ribosomes are highly conserved molecular machines whose core composition has traditionally been regarded as invariant. However, recent studies have reported intriguing differences in the expression of some ribosomal proteins (RPs) across tissues and highly specific effects on the translation of individual mRNAs. To determine whether RPs are more generally linked to cell identity, we analyze the heterogeneity of RP expression in a large set of human tissues, primary cells, and tumors. We find that about a quarter of human RPs exhibit tissue-specific expression and that primary hematopoietic cells display the most complex patterns of RP expression, likely shaped by context-restricted transcriptional regulators. Strikingly, we uncover patterns of dysregulated expression of individual RPs across cancer types that arise through copy number variations and are predictive for disease progression. Our study reveals an unanticipated plasticity of RP expression across normal and malignant human cell types and provides a foundation for future characterization of cellular behaviors that are orchestrated by specific RPs.

Poster | 21

Mycobacteria-Dictyostelium RNAseq reveals transcriptional pathways essential during the infection course

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Tuberculosis remains the most pervasive infectious disease and the recent emergence of multiple drug-resistant strains emphasizes the need for more efficient drug treatments. We use an integrated approach to dissect and model the relationship between mycobacteria and their host. The experimentally versatile Dictyostelium discoideum – M. marinum infection model provides a powerful system to study mycobacteria pathogenicity which can also be used to identify new anti-infective chemicals. Now, we are using the technological developments in high throughput RNA-sequencing to determine transcriptional signatures triggered by mycobacteria. A full analysis of Dictyostelium -M. marinum 'contact' experiment (mixing both organisms for 4 hours at MOI 400) provided a fingerprint of the transcriptome of the host cell in the presence of mycobacteria, and helped us identifying specific markers of the presence of intracellular mycobacteria (GO term: chemotaxis, actin binding, phagolysosome,…). Additionally, a time-resolved transcriptomic analysis of Dictyostelium during infection, covering the critical stages of entry, establishment of a permissive niche, and proliferation was performed to decipher the different host pathways impacted during the mycobacterial infection course. These results will be complemented with the intracellular mycobacterial transcriptome that will allow us to capture the overall transcriptome of the host-pathogen during the infection course. The altered transcriptional signatures caused by the addition of a collection of anti-infective compounds, previously identified by screening on an amoeba – M. marinum infection model, will help to identify their molecular targets and lead to an extensive bio-informatic analysis to build metabolic maps.

Poster | 15

Identification of bacterial cell cycle dependent oscillations by untargeted isotope-dilution mass spectrometry based metabolomics

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A complex regulatory circuit governs timely progression of bacteria through the cell cycle. In recent years, key genetic components of this system have been uncovered, and a large cell-cycle dependent transcriptional program was identified. However, although many decisions on the path to cell division ultimately depend on the metabolic state, global measurement of actual metabolic changes during the bacterial cell cycle are essentially lacking. Here, we developed an untargeted isotope dilution mass spectrometry based approach to follow quantitative changes of hundreds of metabolites throughout the cell cycle of synchronized Caulobacter crescentus cells, a model bacterium for studying cell cycle progression. We observe global changes of metabolite pools as a function of the cell cycle, and a discrete metabolic footprint accompanies the transition from G1 to S-phase to accommodate apparent changing metabolic demands. Moreover, the robust and pronounced oscillations of many identified metabolites make them excellent candidates for second messengers directly involved in cell-cycle control. We anticipate that this study provides a valuable resource for advancing our understanding of metabolic regulation of cell cycle progression.

Poster | 99

In vitro studies of the effect of multiple binding sites on the transcription factor binding affinity

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The quality of models of gene expression, and of transcription in particular, will benefit widely from our knowledge of binding constants. This data can be obtained in a fast and high-throughput fashion using MITOMI, a microfluidics platform for measuring binding affinities in vitro [1].

My SystemsX.ch IPhD project concerns transcriptional regulation in yeast. The question is whether there is an effect of multiple transcription factor (TF) binding sites, in close proximity within promoter regions, on the affinities and occupancy of such promoters. In order to address these questions we employ the MITOMI platform.

We study the binding constants of Pho4p (a basic helix-loop-helix TF) to a library of dsDNA targets with mutated Pho4p binding sites. Fluorescently labeled Pho4p is synthesised in vitro. The affinity and specificity of this TF have been studied previously [1] and serve as a reference point. The metabolic effect of changing the sequence of the promoter region in the area of the binding sites for Pho4p has been studied in our lab [2]. I will show the results that we have obtained thus far, of the affinity measurements of TF-promoter interactions using multi-site libraries of 30bp and 90bp dsDNA targets.

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Poster | 60

Physiological responses of Mycobacterium during phagocyte infection

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Pathogenic Mycobacterium spp., like M. tuberculosis or its close relative M. marinum, enter phagocytic host cells and form a replication-permissive niche called the Mycobacterium-containing vacuole (MCV). In the frame of the HostPathX project, we use the Dictyostelium model to analyze by dual RNAseq the transcriptional changes underlying physiological responses of M. marinum and host phagocytes in the course of an infection.

Mycobacteria require iron for extracellular as well as for intracellular growth. To this end, the bacteria produce specific siderophores called mycobactins to acquire this micronutrient. Here, we focus on the role of metal ions and mycobactins for growth and virulence of M. marinum. Using the specialized phage transduction protocol established in the lab, we constructed a defined M. marinum deletion mutant strain, ΔmbtB, lacking a mycobactin biosynthesis gene. The mutant is severely defective for growth in vitro and in host cells. Moreover, we isolated two forms of mycobactins from M. marinum, hydrophobic MBT and water-soluble cMBT, both of which improve the in vitro growth of Mycobacterium spp. Current studies aim at deciphering the impact of metal ion utilization on the transcriptional level, as well as the intracellular route(s) by which iron is scavenged and acquired by the pathogen.

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Genetic approaches to probe Mycobacterium responses during phagocyte infection

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The causative agent of tuberculosis, Mycobacterium tuberculosis, and its close relative M. marinum manipulate macrophages and amoebic host cells to create a replication-permissive compartment termed the Mycobacterium-containing vacuole (MCV). The identity of cellular compartments is co-determined by phosphoinositide (PI) lipids. The PI pattern is also a crucial trait of MCVs, which is modulated by bacterial phosphoinositide phosphatases.

The HostPathX project aims to generate transcriptional profiles of Dictyostelium amoeba infected with M. marinum, both WT and mutant strains, to define the gene expression patterns occurring in the course of an infection. To generate defined M. marinum deletion mutant strains, we established an efficient specialized phage transduction protocol and targeted the genes encoding mycobacterial PI phosphatases. Thus, we constructed mutants lacking one or all three bacterial PI phosphatases, PtpA, PtpB and SapM. These mutant strains are defective for intracellular replication in macrophages or amoeba, and their escape from MCVs to the cytoplasm was reduced compared to wild-type M. marinum. Moreover, MCVs containing M. marinum lacking PtpA, SapM or all three PI phosphatases accumulate significantly more PtdIns(3)P compared to MCVs containing the wild-type strain. Ongoing studies address the impact of the bacterial PI phosphatases on the bacterial and host cell transcriptomes.

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Integration of heterogeneous omics data using multiplex networks

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Integration of heterogeneous omics data is an extremely challenging task. It is not trivial how to consolidate and analyze genomic data of different types and different scales. We present a method for integrative analysis of heterogeneous omics data using multiplex graphs. A multiplex network is composed of a graph with different layers, it can be seen as a 'network of networks'.

Based on the assumption that the copy number, mutation and methylation status control the expression levels of genes, we construct a mulitplex graph that models each datatype in separate layers. To perform functional interpretation of the data, we further add the gene sets, biological concepts, and phenotype layers. Biological concepts are composed of gene sets and provide high-level functional information. After obtaining the network, we use prize-collecting Steiner Tree to detect communities and maximum flow algorithms to find most probable flow paths.

We have applied our proposed method for integrative analysis using real data. We show that our method successfully identifies genomic and functional modules that are related with cancer subtype classification. With an eye towards personalized medicine, we also applied our method to the functional analysis of drug sensitivity.

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Genetic variation-mediated inference of tissue-specific circadian gene regulatory networks in Drosophila melanogaster

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Circadian rhythms are daily oscillations in behavior, metabolism, and physiology. These patterns are controlled by an internal pacemaker composed of transcriptional and translational feedback loops, which determine rhythmic gene expression in a cell type-specific fashion. Although much is known about the core genetic components of the circadian machinery, the extent to which genetic variation influences circadian gene expression in a tissue-specific manner is still undetermined. To elucidate the molecular determinants of the clock in a tissue-specific manner, we inferred gene expression dynamics from brains, guts, and fat bodies of 151 Drosophila Genetic Reference Panel (DGRP) lines collected throughout the day. We compared them to the white- line which was profiled every two hours for two consecutive days. The experiment resulted in 591 tissue- and genotype-specific transcriptional profiles, allowing us to identify more than 200 white- genes that cycled under clock control and to extend this list to previously uncharacterised tissues where we found 138 genes that oscillated in tissue-specific fashion. Additionally, we identified several DGRP lines with aberrant circadian gene expression. Three lines exhibited a significant phase shift in the expression of the core clock gene timeless, providing a possible mechanism as to how genetic variation influences circadian gene expression. We have also discovered several inter-tissue and time-dependent cis-regulatory variants (eQTLs) that influence circadian rhythm and behaviour. Thus, our collective results elucidate for the first time the effect of genetic variation on both circadian and tissue-specific gene expression programs in the fly, providing unique insights into the underlying regulatory networks.

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Metabolic network prediction of species abundances in a synthetic microbial community

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Functional analysis of microbial communities is important for a host of industrial biotechnology and ecological applications. Constrained-based metabolic models (e.g. flux balance analysis FBA) have been used for describing the phenotype of single microbial species. Recently, these methods have been extended by consideration of interactions between species and their environment, thus proving new insights into metabolic aspects that shape community structure.

We report individual metabolic network models of a synthetic microbial community composed of five species commonly found in soil (Bacillus subtilis, Pseudomonas fluorescents, Pseudomonas stutzeri, Streptomyces coelicolor) and the human gut (Escherichia coli). These were integrated into a multi-compartment metabolic network where each participant is represented as a different compartment that facilitate exchanges among species. This multi-compartment network was integrated into a dynamic extension of FBA (dFBA) considering nutrient uptake kinetics to predict dynamic interactions and changes in the microbial community composition. We adopt a systems biology approach to unravel the metabolic patterns of microbial communities towards the development of spatio-temporal dynamic models where metabolic exchanges are affected by naturally heterogeneous distribution of nutrients such found in soil.

Poster | 9

Systems analysis of mammalian forebrain development

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The cerebral cortex of mammals is composed of billions of neurons (in humans 10^9) organized into functionally distinct layers. The different types of neurons originate from what has been proposed to be a homogeneous pool of neural stem cells (NSCs). We have undertaken a systems biology approach to understand development of the mammalian cerebral cortex, to elucidate the mechanisms controlling neuronal fate and differentiation (NeuroStemX). Through collaborative wet biology and computational modeling approaches we are deciphering the signaling and transcriptional networks that regulate the formation of cerebral cortical neurons. The control of these networks modulates the regimental differentiation and characterization of the NSCs, to pattern the complex six-layered structure of the cerebral cortex. Our hypothesis and preliminary data suggest that NSCs, rather than being homogeneous, are a heterogeneous population that vary in their transcriptional output over time and this renders them sensitive to extrinsic and intrinsic cues. The integration of these intrinsic and extrinsic signals controls neuron production and fate. A comprehensive understanding of transcriptional regulation and its interplay with an ensemble of upstream factors will pave the way for regeneration of cortical neurons and structures following disease and could have implications for cellular therapy and drug screening. We have isolated NSC, progenitor, and newborn neuron populations, generated RNA for sequencing and are experimentally analyzing the predicted regulatory nodes controlling neuronal cell fate. From the global transcriptomes, we have initially focused on one, as yet less explored signaling pathways in the brain, Hippo Pathway and its downstream effectors.

Poster | 73

Identifying molecular targets of drugs using an integrative network analysis of molecular interactions and transcriptomic data

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The identification of the molecular targets of compounds has great importance in drug discovery and drug re-purposing for understanding mechanism of action (MoA) and off-target effects. Many computational methods have been developed for this purpose using transcriptomics data. In this work, we developed Systems Analysis and Learning for inferring Modifiers of Networks (SALMON), a novel method for identifying protein targets of drug compounds. SALMON integrates protein-protein and protein-gene interaction networks to produce the protein-gene network, and employs a kinetic model of the PGN. Proteins targets are scored based on the dysregulation of the PGN, according to the deviations of the gene expression from the model prediction, caused by the drug treatment. In our case studies of three different datasets from human and mouse cell lines, SALMON significantly outperformed the state-of-the-art method DeMAND and differential gene expression analysis in predicting known drug targets. Moreover, SALMON was able to differentiate multiple classes of drugs based on their known MoA, more accurately than the other methods. SALMON is available freely by request.

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REMI: constraint-based method for integrating relative expression and relative metabolite levels into a thermodynamically consistent metabolic model

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Flux balance analysis (FBA) allows steady-state flux predictions using optimization principles and often does not result in a unique steady-state flux distribution. Therefore, integration of omics data, such transcriptomics, metabolomics has been employed as additional constraints to reduce the solution space of feasible flux phenotypes. Here, we present a computational method, termed REMI, which integrates relative expression along with relative metabolomics into genome-scale (GS) metabolic models to estimate the differential fluxes at GS level. First, we integrated relative expression data into an E.coli GS model using our approach and an existing GX-FBA method [1 2]. The results of our method are in more agreement and robust with experiment as compared to GX-FBA, because our method facilitates alternative solution enumeration. High frequency solutions analysis between the alternatives may guide in understanding of a biological system physiology. Furthermore, to further reduce the flux space and obtain predictions closer to actual physiological state first we add thermodynamic constraints into models and then employed relative expression as well as relative metabolomics as additional constraints [3]. The constraint model, resulted in reduced feasible flux space as one can expect, and predicts flux distributions that were in agreement with experiment

Poster | 56

Protein-LEGO: a scalable strategy to dissect protein-genome interactions

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In order to understand the individual and combinatorial contribution of chromatin- and DNA- binding domains in vivo, a representative number of genome-wide binding measurements is required. This includes numerous instances from the same domain family (from different proteins), and also non-functional versions as controls. Current Chromatin Immunoprecipitation (ChIP) methods that require antibodies do not provide the required specificity and would not be feasible for the envisaged number of targets. The first challenge is to establish a novel strategy that allows to measure binding of individual protein domains in vivo at large-scale and in a reliable manner.

We developed parallel recombination-mediated biotin-tagging (PaRBiT) that combines expression of engineered reader domains from a defined genomic site, inserted by recombinase-mediated cassette exchange (RMCE), with in vivo biotin-tagging and parallel, barcoded chromatin immunoprecipitation using streptavidin (biotin-ChIP). This ensures identical, stringent and reproducible ChIP conditions to identify genome-wide binding for multiple domains in parallel, circumventing antibody-affinity and -specificity discrepancies occurring in standard ChIP procedures.

Currently, we are prototyping the first steps of PaRBiT using domains known to bind methylated and unmethylated DNA. Prototyping includes generation of targeting vectors, testing the influence of promoter strength, linker length, biotin tag position and eGFP presence by using our standard recombinase-assisted mapping bio-tag proteins (RAMBiO) approach. These preliminary attempts will allow us optimising PaRBiT for the proposed large-scale measurements.

Poster | 80

Systems phytohormone responses to mitochondrial proteotoxic stress

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Mitochondrial function is controlled by two separate genomes. This feature makes mitochondria prone to proteotoxic stress in case a stoichiometric imbalance occurs in the protein complexes that perform oxidative phosphorylation, which consist of both nuclear- and mitochondrial-encoded proteins. Such a proteotoxic stress is known to induce the mitochondrial unfolded protein response (UPRmt) in animals. It is unknown whether UPRmt occurs in plants. Here, we repressed mitochondrial translation in Arabidopsis thaliana, through either chemical or genetic interference. Mitochondrial proteotoxic stress activated a plant-specific UPRmt and elongated the lifespan of plants. The plant UPRmt pathway is reliant on hormone (ethylene, auxin, jasmonate) signaling, establishing phytohormones, as bona fide plant mitokines. Our data ascertain that mitochondrial protein quality control pathways, such as the UPRmt, are conserved in plants and that hormone signaling is an essential mediator that regulates mitochondrial proteostasis.

Poster | 41

Learning the high-dimensional immunogenomic features that predict public and private antibody repertoires

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Recent studies have revealed that immune repertoires contain a substantial fraction of public clones, which are defined as antibody or T-cell receptor clonal sequences shared across individuals. Due to their increased occurrance within the population, public clones have been identified as potential biomedical targets. As of yet however, it has remained unclear whether public clones possess predictable sequence features that separate them from private clones, which are believed to be generated largely stochastically. This knowledge gap represents a lack of insight into the shaping of immune repertoire diversity. Leveraging a machine learning approach capable of capturing the high-dimensional compositional information of each immune receptor sequence, we detected predictive public- and private-clone-specific immunogenomic differences, which allowed the prediction of public and private status with 80% accuracy in both humans and mice. Our results unexpectedly demonstrate that not only public but also private clones possess predictable high-dimensional immunogenomic features. Our support vector machine learning model could be trained effectively on large published datasets (3 million clonal sequences) and was sufficiently robust for public clone prediction across studies prepared with different library preparation and high-throughput sequencing protocols. In summary, we have uncovered the existence of high-dimensional immunogenomic rules that shape immune repertoire diversity in a predictable fashion. Our approach may pave the way towards the construction of a comprehensive atlas of public clones in immune repertoires, which may have applications in rational vaccine design and immunotherapeutics.

Poster | 81

Protein interaction perturbation profiling at an amino acid resolution

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Identification of genomic variants in healthy and diseased individuals continues to rapidly outpace our ability to functionally annotate them. As such, techniques that both systematically assay the functional consequences of nucleotide resolution variation and can scale to hundreds of genes are urgently required. To address this, we designed a novel, sensitive yeast two-hybrid based “off switch” for positive selection of interaction disruptive variants from complex genetic pools. Combined with massively parallel programmed mutagenesis and a sequencing readout it enables systematic profiling of protein interaction determinants at an amino acid resolution. We defined >1,000 interaction disrupting amino acid mutations across eight subunits of the BBSome, the major human cilia protein complex associated with the pleiotropic genetic disorder Bardet-Biedl-Syndrome. These de novo high resolution interaction perturbation profiles provided a framework for interpreting patient derived mutations across the entire protein complex, highlighting how the impact of disease variation on interactome networks can be assessed systematically.

Poster | 5

Interaction of Tissue and Circadian Transcriptional Regulatory Landscapes

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Temporal control of physiology requires the interplay between gene networks involved in daily timekeeping and tissue function across different organs. The circadian clock ticks in virtually all cells of the body and synchronizes cellular processes with environmental cycles. In addition to this ubiquitous oscillator, different tissues express distinct transcriptional programs. How the circadian oscillator interweaves into these transcriptional programs is not well understood. Here we disentangled temporal and tissue regulatory landscapes at multiple layers of gene regulation by examining mouse tissues with intact or disrupted clock over time. Our analysis integrated new and published data, combining chromosome conformation, DNase-I hypersensitivity, transcriptome, and nuclear proteome to identify regulatory modes underlying rhythmic gene expression in subsets of tissues. Analysis of genes rhythmic in only one tissue uncovered two distinct regulatory modes underlying tissue-specific rhythms: 1) tissue-specific rhythmically active transcription factors, which regulated genes underlying feeding-fasting rhythms in liver and sodium homeostasis in kidney; 2) co-localized binding of clock and tissue-specific transcription factors at distal enhancers. Chromosome conformation capture in liver and kidney identified liver-specific chromatin loops that recruited clock factors to promoters in a tissue-specific manner. Furthermore, this looping was remarkably promoter-specific, nearby alternative promoters with differential temporal outputs formed distinct chromatin loops. These findings suggest that precise chromatin folding enables the clock to regulate rhythmic transcription of specific promoters to output temporal transcriptional programs tailored to different tissues.

Poster | 39

The determinants of the microbiome associated with IBD phenotype

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Crohn's disease (CD) and ulcerative colitis (UC), the two common phenotypes of clinical inflammatory bowel disease (IBD), generally affect over 2.5 million people with an increasing prevalence. They have both overlapping and distinct clinical pathological features which makes diagnosis a challenge for physicians. A decade of microbiome studies suggests that particular components of the intestinal microbiota producing continuous antigenic stimuli are key players for initiating, maintaining and determining the disease phenotype. In this study, we aimed molecularly to profile the intestinal microbiota of phenotypically well-characterized Swiss IBD cohort patients as well as newly recruited IBD patients with non-IBD subjects collected clinically in a longitudinal study. We deeply characterized the microbiota of IBD patients and non-IBD specifically accounting for clinical and environmental factors (including treatment, alcohol consumption, and tobacco use) from 2200 biopsy samples of ~600 patients thus building one of the largest cohorts covering sequence data generated. Our findings revealed that CD and UC are two distinct intestinal disorders at the microbiome level. Dysbiosis observed between disease groups results from a combination of demographic information, inflammation status, drug response, and disease trajectory, each exerting different impacts on the gut microbiota composition of individuals. Although UC and CD patients share many epidemiologic, immunologic, therapeutic and clinical features which make difficult to dissociate the disease status, our results propose microbiomarkers to discriminate between the CD and UC patients.

Assessing the impact of S-palmitoylation on the lipidome of mammalian cells

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Eukaryotic cells have hundreds to thousands of different lipid species, whose specific subcellular distribution is tightly regulated. The need to control lipid diversity and distribution is such that many human diseases are linked to perturbations of lipid homeostasis (obesity, diabetes, lysosomal disorders, atherosclerosis, neuropathies and others).

In this project we aim at understanding the crosstalk between lipid metabolism and signaling. We focus on the interplay between S-palmitoylation and lipid homeostasis, a rather unexplored area despite the fact that many proteins involved in lipid homeostasis are known to be S-palmitoylated or have been found as S-palmitoylation candidates in proteomics studies.

S-palmitoylation, the only known reversible lipid post-translational modification, is the covalent attachment of a C16 acyl chain to specific cysteine residues in the target protein. Here, we examine the lipidome of a collection of knock-out HAP1 cell lines where each of the 23 protein acyltransferases-coding genes and the 2 acyl protein thioesterases-coding genes has been individually turned off. Our experimental approach includes (i) growing and collection of the cells, (ii) total lipid extraction using MTBE as organic phase, (iii) mass spectrometry-based lipidomics, and (iv) statistical analysis and validation. Our detailed strategy, statistics approach and preliminary results are discussed.

Medical Systems Biology

Chair:
Patrick Matthias
Friedrich Miescher Institute
Basel

Speaker

Studying the yeasts of yesterday to generate the beer yeasts of tomorrow

Kevin Verstrepen

Systems Biology Laboratory, VIB Center for Microbiology, Leuven, Belgium; Laboratory of Genetics and Genomics, KU Leuven, Belgium; Leuven Institute for Beer Research, Belgium

The common brewer's yeast Saccharomyces cerevisiae is used in a broad range of industrial applications, from the production of beer, wine and bread to biofuels and pharmaceuticals. Interestingly, there are hundreds of different industrial yeast strains, but their origins and specific characteristics are largely unknown. We combined large-scale phenotyping with genome sequencing to track the genealogy and evolution of today’s industrial yeasts. Using this knowledge allowed us to set up large-scale breeding programs to generate superior variants that increase production efficiency and expand the range of yeast-derived products and aroma’s, allowing more efficient beer fermentation, production of superior beers and the creation of novel products.

Speaker

Use of massively parallel sequencing technologies to identify somatic mutations

Peter Campbell

Cancer Genome Project, Wellcome Trust Sanger Institute, United Kingdom

Massively parallel sequencing technologies have revolutionized the field of cancer genomics. On a single platform, it is now possible to identify all somatically acquired mutations of all classes in a given cancer sample in real time. However, a number of challenges to interpreting the data exist, and necessitate the development of carefully tested bioinformatic algorithms. I will present an overview of our approaches for handling the data, focusing on the practical issues, common artefacts and challenges of current methodologies.

Speaker

Deciphering Host-Virus Interactions to Cure HIV

Karin J. Metzner

University Hospital Zurich, Switzerland

A cure for the HIV epidemic remains elusive despite the highly effective antiretroviral therapy. The existence of the viral reservoir in HIV infected individuals is the major hurdle towards achieving cure. HIV establishes this viral reservoir early in infection and can persist there for an unlimited time. Before cure strategies can be successfully devised and implemented, some open questions pertaining to the viral reservoir remain to be answered: How stable is the viral reservoir? Which host and viral factors influence its stability? In our SystemsX project we studied the decay rates of the viral reservoir in more than 1,000 patients in the Swiss HIV Cohort Study; all successfully treated for >5 years. Surprisingly, the dynamics of the viral reservoir are far more variable than expected. This and possible underlying pathomechanisms will be discussed.

Speaker

A combined experimental and computational strategy identifies key cellular mechanisms for proliferation in pre-erythrocytic malaria parasites

Volker Heussler[1], Rebecca Limenitakis[1], Ellen Bushel[2], Anush Chiappino-Pepe[3*], Julian C. Rayner[2], Oliver Billker[2], Vassily Hatzimanikatis[3]

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The *Plasmodium* liver stage represents a bottleneck in the parasite life cycle and has great potential to be exploited as a target for both drugs and vaccines. Despite this, only relatively small numbers of liver stage-essential genes have been identified. Using a high-throughput knockout screening approach, we are seeking to identify new genes that have key roles in pre-erythrocytic development. To do this we have co-transfected pools of barcoded gene knockout vectors from the *Plasmo*GEM resource and have used Illumina sequencing to monitor changes in barcode abundance at different stages of the life cycle. Having screened and fully evaluated more than 700 *Plasmodium* genes, we have already identified close to 100 knockout parasites that have a significant phenotype during liver stage development.

Integrative analysis of this data can lead to the identification of biological mechanisms that explain the observed phenotypes and that provide testable hypotheses for further discoveries. Metabolic modelling can cope with the tangled and versatile metabolism of the malaria parasites, and hence is a compelling approach for understanding the parasites physiology. We predict *in silico* and test *in vivo* lethal knockouts and synthetic lethal pairs in the blood and liver stages of the malaria infection. We performed computational analyses on a newly developed genome-scale model of the malaria parasite *Plasmodium berghei* (iPbe) using the high-throughput gene knockout data generated in the PlasmoGEM project. The comparison between data and gene essentiality predictions allow the understanding of the parasite's physiology in the blood and liver stages. We identified the thermodynamic bottlenecks, genetic interactions, and the accessibility to nutrients behind the phenotypes. When we simulate in iPbe the hypothesised physiology, we achieve an 80% consistency between the prediction of essential genes and the experimental data. This result indicates that our model iPbe is a valuable framework for the generation of testable hypothesis on antimalarial targets.

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Metabolic modeling of Toxoplasma gondii: toward a tachyzoite-specific network

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Toxoplasma gondii is a ubiquitous obligate intracellular parasite with the remarkable ability to infect virtually all warm-blooded animals. The complex life cycle of this parasite takes place in a wide range of host cell types in intermediate hosts, including humans, and undergoes a sexual phase of development only in the intestine of a definitive felid host. To adapt to these distinct niches, considerable remodeling of metabolic pathways is thought to occur upon stage-conversion. Computational models have emerged as an indispensable tool to investigate these complex changes following developmental and environmental transitions.

Here, we present a well-curated stage-specific model, capable of accurately predicting novel and experimentally observed phenotypes. The study capitalizes on the existing genome-scale reconstruction of T. gondii, ToxoNet1[1], the CRISPR-based genome-wide screen for genes contributing to parasite fitness[2] and gene expression data from various developmental stages. The tachyzoite-specific model, that incorporates tachyzoite-specific RNA-Seq data, exclusively predict the metabolic capabilities and nutritional requirements of this fast-replicating stage. Future refinements of this model could help us investigate the unknown physiologies of T. gondii in its latent and sexual life cycle stages, and understand the metabolic changes that drive and sustain stage transitions.

[1] Tymoshenko, et al. "Metabolic needs and capabilities of Toxoplasma gondii through combined computational and experimental analysis." PLoS Comput Biol 11.5 (2015): e1004261.
[2] Sidik and Huet, et al. "A genome-wide CRISPR screen in Toxoplasma identifies essential apicomplexan genes." Cell 166.6 (2016): 1423-1435.

Short talk | 104

Detecting localized amino acid kinetics through mass spectrometry imaging of stable isotopes

Zita Soons[1], Martijn Arts[1], Shane Ellis[1], Gert Eijkel[1], Ludwig Dubois[1], Tilman Hackeng[1], Luc van Loon[1], Ron Heeren[1], Steven Olde Damink[1, 2]

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Mass spectrometry imaging (MSI) simultaneously detects and identifies the spatial distribution of numerous molecules throughout tissues. Currently, MSI is limited to providing a static and ex-vivo snapshot of highly dynamic systems where molecules are constantly synthesized and consumed. Here we demonstrate an innovative MSI methodology to study dynamic molecular changes of amino acids within biological tissues by measuring dilution and conversion of stable isotopes in a mouse model [1]. We evaluate the method specifically on hepatocellular metabolism of the essential amino acid L-Phenylalanine, associated with liver diseases. Crucially, the method reveals the localized dynamics of L Phenylalanine metabolism, including its in vivo hydroxylation to L-Tyrosine, and co-localization with other liver metabolites in a time course of related samples from different animals. This method thus enables the dynamics of localized biochemical synthesis to be studied directly from biological tissues. In this presentation, we will also show results from a follow-up study, in which we demonstrate the application to visualize localized tumor metabolism in relation to hypoxia.

[1] M. Arts, Z. Soons, S.R. Ellis, K.A. Pierzchalski, B. Balluff, G.B. Eijkel, L.J. Dubois, M. Gijbels, H.M.H. van Eijk, Natasja G. Lieuwes, S.M. Agten, T.M. Hackeng, L.J.C. van Loon, R.M.A. Heeren, S.W.M. Olde Damink, Angewandte Chemie 56, 7146-7150.

Poster | 88

A Systems Biological Approach to the Anti-Diabetogenicity of High Density Lipoproteins

Miroslav Balaz[1], Edlira Luca[2], Mustafa Yalcinkaya[3], Mathias Cardner[4], Sandra Goetze[1], Lucia Rohrer[3], Jan Krützfeldt[2], Christian Wolfrum[1], Arnold von Eckardstein[3]

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Low blood levels of HDL-cholesterol increase the risk of diabetes mellitus type 2 (T2DM). HDL particles exert several potentially anti-diabetic activities but neither their relative importance nor their mediators are known. Understanding of these structure-function-disease relationships is essential to exploit HDL for prevention and treatment of T2DM. We isolated HDL particles from the plasma of 25 healthy subjects and 47 patients with T2DM to characterize their protein and lipid abundances by mass spectrometry as well as their functionality towards cells relevant for the pathogenesis of T2DM. We recorded the ability of HDL to inhibit the apoptosis of pancreatic beta cells, to modulate mitochondrial respiration in brown adipocytes and to regulate mitochondrial potential as well as phosphorylation of Akt and Acetyl-CoA carboxylase in myocytes. The data on clinical and anthropometric features of the patients, the protein and lipid composition as well as functionality of HDL are integrated to identify components and functions, which differentiate HDL of patients and controls. Structural components of HDL that best discriminate patients and controls as well as function and dysfunction of HDL will be followed-up by experimental and clinical studies to unravel their mechanism and clinical utility as biomarkers, respectively.

Poster | 62

Exploring cellular phosphorylation network responses to DNA damage using targeted mass spectrometry

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Following DNA damage, cells activate signaling networks which coordinate cell cycle checkpoints, DNA repair and when necessary, cell death. The modification of proteins by phosphorylation has been demonstrated to play a central role in conveying the DNA damage signal and in coordinating the cellular response. Yet, which and how protein kinases act to coordinate context-specific DNA damage networks has remained an open question. To meet this aim, we identified a qualitative set of nodes in a network representing kinases and phosphoprotein substrates, which can be measured reproducibly by targeted mass spectrometry. Phosphoprotein nodes in the signaling network were measured by selected reaction monitoring (SRM) and perturbed by small molecules, to assess the impact of prior kinase inhibition on the response to a specific type of DNA lesions, double-strand breaks (DSBs). From the analysis of this large compendium, we found that in a well-defined context of cell line and treatments, only few selected kinase activities were involved in the phosphorylation response to DSBs. To generate new hypotheses as to how these kinases act in concert, we developed Boolean network models for this context-specific signaling network. Taken together, these data have suggested several phosphoprotein nodes in the DNA damage network that are context sensitive, adding another layer of complexity to the DNA damage response.

Poster | 101

AneuX - Modeling shape as a biomarker for instability of intracranial aneurysms

Philippe Bijlenga[1], Sven Hirsch[3], Brenda Kwak[2], Brigitte von Rechenberg[4], Niels Kuster[5], Daniel A Rüfenacht[4]

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Intracranial aneurysm is a disease of the vessel wall resulting in deformation of the vascular lumen. The disease is life-threatening if the process of deformation remains active. The disease is prevalent (2-5% of the population) and has a high socio-economic impact.
It is accepted that wall shear stresses induced by the flowing blood and cyclic stretching by pulse waves drive the vascular remodeling. In turn, the biological reactions of the vessel wall modify the shape of the aneurysm, visible to modern routine imaging procedures. This suggests that the aneurysm 3D-shape is the visible result of complex pathological processes, characterizing the disease status.
AneuX tested the hypothesis that aneurysm 3D-shape can be used as in image biomarker for disease status. A biological track integrated the basic biological findings of mechano-biological transduction into a fluid structure growth model. The model was refined using experimental observations made on endothelial cells cultured and exposed to different shear stresses and on human aneurysm domes collected during surgery. Endothelial cell cytoskeleton organization and transcriptome as a function of shear stress and vessel wall constituent at different disease stages were measured and integrated in the bio-mechanical model. A clinical track collected and organized clinical evidence using machine-learning support considering shape descriptors. It was shown that a simple model using shape remains optimal in predicting aneurysm stability. AneuX developed a data archiving system allowing the integration and exploration of clinical information and biological samples as well as experimental data generated exploring molecular, cellular and organ level biology globally.

A personalized model of cholesterol homeostasis mechanisms based on trans-omics data integration

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In individuals, heterogeneous drug response phenotypes result from a complex interplay of dose, drug specificity, genetic background, and environmental factors, thus challenging our understanding of the underlying processes and optimal use of drugs in the clinic. Here, we present an approach that combines mass spectrometry-based quantification of molecular drug response phenotypes with mechanistic modeling to explain cellular drug responses. This approach was applied to cellular cholesterol regulation, a biological process with high clinical relevance. The elicited drug response phenotypes were quantified after perturbation by various targeted pharmacologic or genetic treatments in a panel of four cell lines. From the results, we generated cell-line-specific models that identified the processes beneath the idiotypic intracellular drug responses. This revealed that the cellular processes were qualitatively conserved and that the heterogeneous drug response resulted from the quantitative variability of the functional interactions. Hence, this study demonstrates how combining proteomic and metabolomic data with mechanistic modeling can extend our understanding of drug effects on well-studied biological processes.

Poster | 16

Perturbations in protein stoichiometric relationships as a novel class of biomarkers

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Recent advances in mass-spectrometry (MS) based proteomics have allowed for a higher degree of measurement reproducibility and a higher precision in protein quantitation. This, as a corollary, also supports novel conceptual approaches in data analysis. Here, we describe a method that indirectly assesses the status of a protein complex based on the quantitative relationships of its components. Defined ratios of protein quantities are frequently an essential element of complex stability and can thus serve an indicator of its functional state. We applied the new method to investigate disease-associated perturbations in stoichiometries using the SWATH-MS proteomics data for 48 and 39 patients with breast and prostate cancer, respectively. Jointly, we found nearly 300 protein pairs that were annotated as stable interactors in public databases and that had a strong perturbation signal when compared to non-disease samples from the same tissue. This protein set had an even stronger enrichment in known cancer proteins than the top top up- and down-regulated individual proteins. Moreover, among the significant pairs were also less characterized signaling proteins with links to cancer pathways. Ratio of some of the protein pairs, such as the metabolic enzyme lactate dehydrogenase isoforms A and B (LDHA and LDHB) additionally showed a significant correlation with the disease grade and patient survival. The observed association of protein quantitative ratios with a disease status offers an opportunity for developing a novel class of biomarkers with contextual information.

Poster | 90

Single-cell transcriptomic data analysis unveils a heterogeneous and dynamic landscape of tumor infiltrating CD8 T cells

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CD8+ T cells are known to transition through different states depending on their environment and signals from other cells. However, the landscape of tumor infiltrating CD8+ T cells is still not fully elucidated. Here we collected and analyzed single-cell RNA-Seq data of tumor infiltrating CD8+ T cells from mouse and human. Our unsupervised approach recapitulates most known CD8+ T cell subtypes, including exhausted effector-like, Pdcd1+ Tcf7+ memory-like, naïve/central-memory-like and cycling cells. In addition, we observed a small population of cells displaying low expression of inhibitory receptors and highly specific expression of Klrg1 (as in short-lived effector cells) and Gzma, which we experimentally validate with flow cytometry. TCR reconstruction and pseudo-time ordering enables us to follow at the single cell level the differentiation process of single clones and predicts distinct pathways towards effector/exhausted state. To enable rapid and intuitive visualization and exploration of these high-dimensional and information-rich data, we developed an online tool, which may guide future investigations of the diversity of tumor infiltrating CD8+ T cells.

Identifying and targeting key cellular mechanisms for proliferation in Plasmodium parasites: a combined experimental and computational strategy

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Recent advances in cell genome editing techniques enable the generation of high-throughput gene knockout data in the malaria parasites in vivo. Integrative analysis of this data can lead to the identification of biological mechanisms that explain the observed phenotypes and that provide testable hypotheses for further discoveries. Metabolic modelling can cope with the tangled metabolism of the malaria parasites, and hence is a compelling approach for understanding the parasites physiology.

In this study, we present a combined experimental and computational approach that suggests cellular mechanisms for targeting the malaria parasites. We predict in silico and test in vivo lethal knockouts and synthetic lethal pairs in the blood and liver stages of the malaria infection. We perform computational analyses on a newly developed genome-scale model of the malaria parasite Plasmodium berghei (iPbe), and we use high-throughput gene knockout data generated in the PlasmoGEM project. The comparison between data and gene essentiality predictions allow the understanding of the parasite's physiology in the blood and liver stages. We identify the thermodynamic bottlenecks, genetic interactions, and the accessibility to nutrients behind the phenotypes. When we simulate in iPbe the hypothesised physiology, we achieve 80% consistency between the prediction of essential genes and the experimental data. This result indicates that our model iPbe is a valuable framework for the generation of testable hypothesis on antimalarial targets. Overall, the knowledge generated in this framework will serve to tackle more efficiently the malaria parasites' metabolism during infection.

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Skin microbiome of human burn wounds: a model to explore bacterial interactions and impact of treatments.

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Rationale:
Burn infection is the major cause of morbidity and mortality after burn trauma. Any innovative strategy that could curb down the incidence of sepsis in burn patients would be welcome. We hypothesise that burn wound microbiome composition might mitigate the growth of pathogens.

Study design:
Serial microbiome samples of healthy skin and burn wounds were collected from burned patients admitted to the CHUV ICU from June 2015 to March 2017. Bacterial community composition was determined by sequencing specific regions of the 16s rRNA.

Results:
Among the 29 patients with burns >10% TBSA (total body surface area) included in the study, 13 patients suffered from burn wound infections. DNA extraction from healthy as well as burn wound was challenging due to a low amount of bacteria on patient skins after clinical treatments and potential PCR inhibitors. While the inguinal folds exhibit the highest diversity, other burn wound microbiome display a significant decrease in their bacterial diversity during the stay. We further modelize the potential impact of surgical and medical burn wound treatments – considered as pertubators - on microbiome composition using the time-series equation from Stein et al. We found possible interaction between Staphylococcus and Pseudomonas and could show dramatic effect of topical effect as shower and silver containing bandages.

Conclusions:
This study is the first step towards a better comprehension of the bacterial interaction and bacterial resistance to clinical treatments leading to infections.

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Translational activity and preparedness of naïve CD4 T cells

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Naïve T cells circulate in the human body as small, quiescent cells with minimal metabolic activity. Yet, they need to be ready to rapidly respond to antigens and promptly execute a substantial activation program. To investigate the balance between “dormancy” and “readiness”, we globally analyzed protein synthesis rates in naïve and activated T cells using a pulsed SILAC proteomics approach, and estimated absolute copy numbers of 7,800 proteins. In parallel, we sequenced transcripts and estimated copy numbers of mRNAs. We found that naïve T cells contain approximately 500 millions of proteins but only 14,000 mRNAs. The translational activity in naïve T cells was low and most proteins remained stable and were not synthesized within 48 hrs. However, a small subset of proteins was rapidly renewed including components of MHC-I and other cell surface receptors, components of the autophagy machinery and four transcriptional regulators whose murine homologs play a role in maintaining the naïve state of T cells. Despite little protein synthesis, naïve T cells contained enough ribosomal proteins to assemble 400,000 ribosomes. Several highly abundant mRNAs were hardly read off by ribosomes in naïve T cells but already six hours following activation these transcripts were read off at full capacity and the translational output per ribosome increased 8-fold. Thus, naïve T cells are equipped with large numbers of idle ribosomes and mRNAs that are rapidly engaged following stimulation to ramp up the activation program.

Associating HDL proteotype with clinical HDL particle signaling capacity

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The main function of high-density lipoprotein (HDL) particles in the human body is to transport cholesterol from tissues to the liver, so that excessive cholesterol can be eliminated in the bile. High plasma levels of HDL cholesterol are clinically associated with a lower risk of coronary artery disease (CHD) and diabetes mellitus type 2 (T2DM). To date, HDL could not be successfully exploited for prevention or treatment of CHD or T2DM. This is mainly due to a lacking structure-function relationship of the complex HDL particle composition. In the HDL-X initiative we therefore set out to (i) identify components (proteins/lipids) of HDL disturbed in patients with CHD and/or T2DM, (ii) link structural information with phenotypic functionality and ultimately to (ii) validate and exploit HDL-components for treatment and diagnostics. Here we present the first quantitative proteotype analysis of HDL particles sampled from different patient groups. Using Data-Independent Acquisition (DIA) mass spectrometry workflows in combination with spectral libraries we generated a quantitative data matrix of 282 HDL-associated proteoforms across 96 clinical HDL preparations. Together with further lipidomics and functional data generated by the HDL consortium we now have the relevant data in place to start modeling HDL structure function relationships.

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Functional and structural analysis of the BBSome complex in viral infection and beyond

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In an intriguing hijacking of the host machinery, the influenza A virus employs the HDAC6-dependent aggresome pathway for uncoating at the late endosome. The virus uses the C-terminal Znf-UBP domain of HDAC6 and cytoskeletal proteins such as tubulin and actin to break open its viral capsid with the help of dynein and myosin motor proteins (Banerjee et al. 2014). Interestingly, the BBSome, an octameric complex comprising highly conserved Bardet-Biedl syndrome (BBS) proteins with important roles in protein sorting, was recently shown to interact with HDAC6 and to be dependent on similar cytoskeleton and motor proteins (Nachury et al. 2007, Loktev et al. 2008, Liew et al. 2014). Nevertheless, the functional implications of the HDAC6-BBSome interaction in viral infections or other processes remain unexplored. Here we set out to functionally and structurally characterize the HDAC6-BBSome roles in influenza infection. We are currently characterizing individual BBSome subunits as well the entire complex from recombinant or endogenous sources. Moreover, we will structurally define the HDAC6-BBSome interaction and determine influenza infectivity in BBS knockout cell lines. We hope that our studies will illuminate novel roles for an ancient protein complex and provide mechanistic insights into the influenza life cycle with direct therapeutic applications.

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Evolutionary tradeoffs, universal cancer tasks, and the functions of driver mutations

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Cancers continually evolve, with driver mutations conferring a selective advantage. Yet cancers differ in which driver mutations they carry. Comprehending the function of driver mutations and understanding why drugs affect some tumors and not others are pressing fundamental questions. To address these, we apply multi-task evolution theory to large-scale cancer datasets. Multi-task evolution predicts that when tradeoffs exist between several tasks, phenotypes fall on low-dimensional polyhedra, with each vertex specializing in one task. In accordance with the theory, we find that across tissue types, tumor gene expression varies in a continuum bounded by five archetypal gene-expression profiles that each corresponds to a universal cancer task: peroxisome activation, mitochondrial activity & translation, DNA replication & mitosis, interaction with the immune system, invasion & signaling. Some cancers are specialists at one task whereas others are generalists. We further find that driver mutations specialize tumors in one of these tasks. For example, p53 mutations tune gene expression towards the mitosis task and PIK3CA mutations tune tumors towards invasion. Tumors specializing in a task are most sensitive to drugs that interfere with this task. These concepts integrate gene expression, mutations and drug sensitivities into a unifying theory of multi-task cancer evolution.

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Multi-parametric, Single Cell Measurements by Imaging Mass Cytometry for the Classification of Breast Cancer Patients

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Current pathology scoring in breast cancer and subsequent patient risk assessment depend mainly on tissue staining of specific cell type markers. However, these are measured individually, not in relation to each other, and not in a quantifiable manner thus leaving space for improvement. Imaging Mass Cytometry (IMC) can simultaneously measure over 50 antibodies with sub-cellular resolution. Here, we quantitatively compare IMC immunostaining to classic Immunohistochemistry and Immunofluorescence approaches validating its use for clinical classification.

Combined with a novel computational pipeline we used IMC to measure the single cell features and common cell interactions of hundreds of patient samples. Single cell analysis revealed a surprising level of inter and intra-tumor heterogeneity and identify new diversity within known human breast cancer subtypes as well as a variety of stromal cell types that interact with them. Spatially-resolved measurements identified statistically significant interactions between specific cell types and how the organization of these cells changes between tissues of differing pathologic grade. Cell interactions, the 'cell-social-networks' of different tumors, grouped distinct subsets of breast cancer based on their single cell landscape. These topographic biomarkers were correlated to clinical outcome and compared to current clinical classification to assess the ability of single cell measurements to improve patient stratification.

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Identification of lipid species as biomarkers of NAFLD using a systems genetics approach

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As genome-wide association studies (GWAS) may be reaching their limit for discovering genetic determinants of non-alcoholic fatty liver disease (NAFLD), alternative genetic strategies, such as the mouse genetic reference populations (GRPs) may provide both novel and complementary information to identify clinically and biologically important biomarkers of NAFLD. Since accumulation of specific lipids in the liver is the pathophysiologic hallmark of many liver diseases including NAFLD, we aimed to find the lipid biomarkers of NAFLD in serum using the BXD mouse GRP.

Here, we profiled over 120 lipid species across 50 strains of the BXD GRP, fed either chow or high fat diet. By integrating these data with genomics and phenomics datasets, we found QTLs for ~70% of the lipids measured and linked several lipid species to genetic loci for blood lipid levels and associated metabolic traits identified in human GWAS studies. Lipid species from different classes were identified as markers of metabolic status. In particular, we identified 7 triglyceride species as biomarkers of NAFLD in plasma. Four of these—identified as pro-NAFLD biomarkers—showed strong positive correlation with clinical NAFLD readouts (body weight, fat mass, liver mass, cholesterol, glucose, Insulin, ALAT, ASAT), whereas 3 other lipid species—identified as anti-NAFLD biomarkers—showed negative correlation with these phenotypes. These biomarkers were further validated in mouse models of NAFLD and in plasma from NAFLD patients. Hence plasma lipid species can serve as powerful, non-invasive, clinically relevant signatures of metabolic health.

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Measuring the perceived morphological complexity of intracranial aneurysms

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The rupture of intracranial aneurysms is a potentially deadly event. Aneurysm detection is based on imaging techniques, amongst which 3D angiograms deliver the highest quality. Currently, neuroradiologists assess such images only in a qualitative manner, even though it remains unclear how morphological properties relate to the disease status quantitatively.

In an effort to identify suitable descriptors that capture the irregularity of aneurysms, we relate a range of shape descriptors to expert assessments of aneurysm morphology. In a first step, we extracted 3D models of aneurysms from 3D angiographies and calculated geometry indices and moment invariants describing size and shape of aneurysms and surrounding arteries. In a second step, we compared these descriptors to human assessments of irregularity of the aneurysm dome.

Preliminary results are presented based on 134 aneurysm models and 15 raters (5 clinicians, 10 informed laymen). Univariate correlation revealed that curvature-based metrics predict most accurately the human assessment of irregularity (rank correlation: ρ=0.86). This study was performed within the scope of the AneuX project, funded by SystemsX.ch, and received support by SNSF NCCR Kidney.CH.

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A computational framework for systems pathology of prostate cancer

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Personalized medicine relies heavily on the patients' data analysis including but not limited to the genomic datasets that are becoming increasingly more available nowadays. Prostate cancer is the second most frequent cancer type in men, but it is not always possible to make an accurate survival prognosis. Taking these into consideration, prostate cancer will be used as a case study to develop a novel computational framework to search for prostate cancer specific genomic alterations and study how they could improve the stratification of prostate cancer in two classes, significant and insignificant disease.

The new framework will employ machine learning techniques, mainly focusing on pattern detection. A very promising method to be applied is dictionary learning with sparse coding, an efficient tool that has been used in image processing. Briefly, what it can accomplish is to identify genomic alterations that make substantial contributions to variation of complex traits that is not based on exhaustive search and therefore is computationally efficient and can be applied to smaller patient cohorts. Additionally, the framework will be used to integrate different types of genomic alterations from the TCGA Prostate Adenocarcinoma datasets and an independent cohort, the Zurich Prostate Cancer Outcome Cohort study.

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Antibody repertoires under hygiene constraints: from germ-free to increased microbial complexity

Julien Limenitakis, Sandra Rupp, Hai Li, Stephanie Ganal-Vonarburg, Kathy McCoy, Andrew Macpherson

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Microbial colonization of the gastrointestinal tract educates and shapes the development of the immune system. Accordingly, germ-free (GF) mice show an immature immune system with reduced serum immunoglobulin titters of all isotypes except for IgE. These GF mice antibodies may not specifically bind to any member of the microbiota. The exposure to a diverse microbiota is consequently required for a basal regulation of the immune system and the consequences of this exposure in the gut on B cell repertoire are potentially profound.

The recent developments of immunoglobulin repertoire sequencing provide an unprecedented opportunity to unravel new insights in repertoire composition and development at an unprecedented depth.

The aim of this project is to assess, in the context of increasing microbial complexity residing in the gut, the antibody repertoire of B cell populations in the gut (ileum). We observed that gut IgA repertoires in germ-free animals segregate from colonized animals. Interestingly we also observed so-called public clones shared across animals.

Finally, we tested whether an oral gavage or intravenous antigen delivery route in germ-free animals generates different gut IgA repertoires. Our preliminary results suggest that distinct gut IgA repertoires are generated upon exposure to the same antigens delivered from different routes.

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A computational model for influenza vaccine response of stem cell transplant patients

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Seasonal influenza results worldwide in millions of cases of severe illness and several hundred thousand deaths per year, and immunocompromised patients suffering chronic diseases or post-transplantation have a significantly increased mortality. While vaccination is the most effective therapy against influenza, its efficacy is limited in immunocompromised patients, especially early post-transplantation.

We develop a computational model of the vaccine response with the aim to predict the vaccine-induced antibody response in allogeneic hematopoietic stem cell transplant (HSCT) patients, using a minimal set of clinical, immunological and genetic markers. Our model captures the B cell dynamics during primary and secondary immune response and the interactions of B, dendritic and T helper cells. We identified markers that are associated with antibody levels before and after vaccination from two independent, multicenter HSCT patient cohorts. Clinical and genetic markers are mapped onto model parameters, while immunological markers define the initial conditions. Training and testing the vaccine response model on the two HSCT patient cohorts will allow for both an a priori classification of HSCT patients and an identification of novel personalized vaccination strategies.

Such an integrative vaccine response model is a promising approach to understand how to improve vaccination efficacy in immunocompromised patients.

Disease module identification as a DREAM community challenge

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Identification of functional units (called modules or pathways) in gene and protein networks is at the core of many current analysis methods in biomedical research. However, how well different methods perform to uncover biologically relevant modules in different types of genomic networks remains poorly understood. To address this issue, we created the Disease Module Identification DREAM Challenge, which is the first open data competition to rigorously assess module identification methods across diverse gene and protein networks. Over 40 participating teams predicted modules for individual networks as well as integrated modules across multiple networks. Predicted modules were evaluated using a novel approach based on data from disease-relevant genome-wide association studies (GWAS). Since we are employing a comprehensive collection of over 200 GWAS datasets ranging over multiple disease-related human phenotypes, this approach covers a broad spectrum of functional units, many of which have not been annotated previously and might correspond to novel molecular processes involved in disease. In this short talk I will give a brief overview of the challenge and results, including the GWAS-based evaluation method, the best performing module identification methods, and novel disease pathways obtained from the community predictions.

Web: https://synapse.org/modulechallenge

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Systems-wide analysis of the tumor immunome following treatment with a novel antibody drug conjugate

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Cancer cells from a fifth of breast cancer patients overexpress the receptor Her2 but despite the presence of this tumor-antigen nearly 70% of all patients develop drug-resistance to monoclonal antibody therapy Trastuzumab (Tras). Antibody-drug conjugates (ADC) allow for targeted chemoimmunotherapy. We tested a novel ADC bearing a potent anthracycline payload (Tras-PNU) in a murine breast cancer model and compared the anti-tumor efficacy to treatment with Tras and Tras-Emtansine (Tras-DM1), which is currently approved for Her2+ refractory breast cancers. While tumors are resistant to Tras and Tras-DM1, Tras-PNU strongly reduces tumor growth by a CD8 T cell-dependent immune response able to elicit immunologic anti-tumor memory. By performing RNA-seq and gene expression analysis on purified CD45+ tumor infiltrating lymphocytes (TILs), we were able to identify clear immune-related gene signatures that distinguished the responding Tras-PNU from non-responding untreated, Tras and Tras-DM1 treated samples. Lymphocyte clonal analysis from RNA-seq data revealed increased B and T cell clonal diversity and expansion for Tras-PNU treatment, thus highlighting the importance of an adaptive immunity-driven anti-cancer response as a major mode of action with Tras-PNU treatment. In summary, we describe a novel ADC therapy to overcome resistance in breast cancer by promoting long-term immune protection.

The effect of micronutrients on the intestinal microbiota in a gnotobiotic mouse model

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The importance of the microbiota in influencing health and disease is well accepted. Numerous “Western” diseases are associated with a disturbed microbiota. However, the underlying mechanisms remain unexplained. Diet being a major factor shaping the microbiota and host immunity, we addressed the effects of a purified fat-enriched and a starch-enriched diet compared to a conventional plant-based chow on the intestinal microbiota using a gnotobiotic mouse model containing 12 different bacteria.

Metagenomic and metatranscriptomic analysis of the microbiota allowed us to investigate microbiota composition, growth dynamics and gene expression profiles of each of the 12 species under the three diets.

We show that Cl. orbiscindens acquires a growth advantage under the purified diets, illustrated by a faster replication rate and higher abundance. Gene expression profiling shows upregulation of B12 synthesis pathways. Supplementation of vitamin B12 abrogates the autogenous B12 production of Cl. orbiscindens, abolishing its fitness advantage and thereby leading to a decrease in its abundance.

This novel approach allows us to understand subtle mechanisms underlying changes in the microbiota composition and metatranscriptome. Furthermore we depict the importance of micronutrients by tuning the community composition and metatranscriptome by the simple supplementation of vitamin B12.

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Structural characteristics of the human intracranial aneurysm wall prone to rupture

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Intracranial aneurysm (IA) is a disease of the vascular wall resulting in abnormal enlargement of the vessel lumen. IAs are mostly quiescent and asymptomatic, but their rupture leads to severe brain damage or death. Physicians lack adequate tools to safely determine whether an IA is at risk of rupture. The goal of the AneuX project is to use the aneurysm 3D-shape to characterize disease status.

IA domes, ruptured (RIA, N=18) or not (UIA, N=31), have been collected following the clipping of the IA at the Geneva University Hospitals. Domes have been fixed in Formol, embedded in paraffin, sectioned and stained for smooth muscle cells, macrophages, collagen and elastin. Comparisons have been performed using non-parametric Mann-Whitney U test.

Patients and IA dome characteristics are not different between RIAs and UIAs. Histological analysis of aneurysmal wall composition revealed that RIAs have a higher content in macrophages (3.1% vs. 0.4%).

Our results show that the IA wall prone to rupture presents a lower smooth muscle cell and collagen content, independently of the wall thickness, and a higher content in macrophages.

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Evaluation of synthetic oligonucleotide sequences for preventing Salmonella Typhimurium infection

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The pathogen Salmonella enterica serovar Typhimurium (S.Tm) is a common cause of diarrhea. Because the virulence factors T1 and T2 act by manipulating host cell signal transduction and actin cytoskeletal rearrangements, host cell factors are indispensable for S.Tm invasion (Kaiser et al., 2012). To identify host cell factors needed for S.Tm invasion, we previously performed genome-wide RNAi screens in vitro by using a human cell line. The "on-target" effects of the siRNAs identified novel host cell factors involved in S.Tm infection (Kreibich et al., 2015, Andritschke et al., 2016). In addition to these on-target effects, we observed off-target effects (Franceschini et al., 2014). These effects are mediated by a 7mer 'seed sequence' of the siRNAs, ranging from nucleotides 2-8. By quantitative analysis, we found that these off-target effects are more pronounced than the "on-target" effects of an average siRNA sequence. The seed-mediated off-target effects could also be found in a mouse-derived cell line. Here, we are exploring, if this off-target effect can be used to prevent infection. We will present identified sequences in human cells and mouse cells, and discuss our proof-of principle study to assess if such "seed drugs" could applicate in the established mouse model to fight infection.

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Development of an approach to unravel the metabolic interactions in a defined complex microbial consortia

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Most of gut microbiota studies focus on ‘who is there’ but there is a great gap to answer the question ‘what are they doing’. There is to date, no systematic approach to unravel the nature of the metabolic interactions occurring in microbial consortia. This project focuses on the development of an approach to elucidate the exchanges that occur between the members of a defined consortium of medium complexity. The combination of non-targeted metabolomics with in vitro culture allow us to establish an in vitro food network that can be further tested in vivo.

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Improving gene set analysis using networks

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Differential gene expression (DGE) studies often suffer from poor interpretability of their primary results, i.e., thousands of differentially expressed genes. This has led to the introduction of gene set analysis (GSA) methods that aim at identifying interpretable global effects by grouping genes into sets of common context, such as, molecular pathways, biological function or tissue localization. In practice, GSA often results in hundreds of differentially regulated gene sets. Similar to the genes they contain, gene sets are often regulated in a correlative fashion because they share many of their genes or they describe related processes. Using these kind of neighborhood information to construct networks of gene sets allows to identify highly connected sub-networks as well as poorly connected islands or singletons. We show here how topological information and other network features can be used to filter and prioritize gene sets in routine DGE studies. Community detection in combination with automatic labeling and the network representation of gene set clusters further constitute an appealing and intuitive visualization of GSA results.

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Endothelial cell elongation under shear stress - a computational model to consolidate observed cell shape changes

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The endothelium, a single layer of cells that lines all blood vessels, is the principal sensor of hemodynamic wall shear stress (WSS). Changes in WSS are associated with diseases as inflammation, atherosclerotic plaque formation or aneurysms. It has long been established that endothelial cells are elongated under physiological blood flow conditions, but become cobblestone in culture under no flow or low flow conditions. To quantify these changes in cell morphology, we measured the circularity and aspect ratio of porcine aortic endothelial cells cultured under physiological flow conditions (30 dynes/cm2), low flow (2 dynes/cm2) or high flow (80 dynes/cm2) conditions as found typically found in intracranial aneurysms. A static condition was taken as a control. A parsimonious biomechanical cell-vertex model allows us for the first time to explain the observed changes in cell morphology by local changes in the cell boundary tension associated with changes in the architecture of the cytoskeletal network.

This study was performed within the scope of the AneuX project, funded by SystemsX.ch

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Metabolic flux prediction in kidney induced hyperammonemia

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Hyperammonemia is a metabolic condition characterised by elevated levels of ammonia in the blood, which can have serious consequences. The kidney plays a critical role in excreting ammonia but not much is known about its function in hyperammonemia. Systems biology has become a promising tool to understand metabolic diseases, several methods exist to predict metabolic fluxes but they are difficult to calibrate and validate against in vivo data. Here, we developed a method based on elementary mode analysis to study changes in amino acid flux in the kidney in hyperammonemia. A previous computational model of central carbon metabolism was adapted to the kidney by using kidney gene expression data. This model was used to predict amino acid fluxes in healthy and hyperammonemic conditions, which were compared to experimental fluxes in rats. The best predictions were obtained when ammonia transport was used as an objective, and these predictions were improved when specific gene expression data were taken into account for hyperammonemic conditions. Other objectives that resulted in an increase in hyperammonemia include glutamine uptake, serine, arginine and alanine transport. All but serine can act as nitrogen scavenging molecules, which suggests that the kidney might be trying to utilise these amino acids in order to aid removal of ammonia from the blood.

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A systems biology approach for the identification of solute carrier transport systems in vitro

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Membrane transport is an essential physiological function catalyzed by various transmembrane proteins including 300+ Solute Carrier (SLC) transporters. Determining contributions of each type of SLC to overall cellular transport for a given substrate is fundamental for understanding mechanisms regulating homeostasis of physiological solutes. However, this is complicated since substrates are often transported by multiple SLCs with overlapping specificities and differing affinities. We developed a systems biology approach to robustly quantify the contributions of specific SLCs to the aggregate transport of a given substrate based on limited experimental measurements. The established model was built for the L-leucine (Leu) and L-phenylalanine (Phe) carrier-mediated transport system expressed in Xenopus laevis oocyte. With our developed approach, we: (1) quantified the activity of individual components of Leu carrier-mediated transport system under variety of experimental conditions and observed the dominance of uniporters SLC43A2/LAT4 (and/or SLC43A1/LAT3) and the sodium symporter SLC6A19/B0AT1 among nine potentially Leu transporters; (2) predicted the response of the Leu transport system to new stimuli in the presence of various competitive substrates and/or inhibitors; (3) predicted the activity of Phe carrier-mediated transport system; and (4) accurately calculated the behavior of heterologously expressed human SLC6A14/ATB0+ (hATB0+) and SLC43A2/LAT4 (hLAT4). While we applied these strategies to amino acid transport system expressed in Xenopus laevis oocytes, given the appropriate conditions, the developed methodology is applicable to identify a broad range of carrier-mediated transport systems expressed in various cell culture models.

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Dissecting the role of the HDAC6/aggresome pathway in influenza virus infection: VirX

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Histone deacetylase 6 (HDAC6), a lysine deacetylase whose main substrate is alpha tubulin, is a critical factor for infection by influenza A virus (IAV) (Banerjee et al., Science 2014). Thereby, HDAC6 promotes uncoating of IAV and is a proviral factor early in infection. Absence of HDAC6 leads to a reduction in viral titers. The HDAC6 zinc finger domain (ZnF-UBP), which binds ubiquitin, is essential, while the catalytic activity is not required. IAV was found to be loaded with ubiquitin and may mimic the cellular aggresome pathway, for which HDAC6 is essential. Our working model is that HDAC6, together with ubiquitin, dynein and actin/myosin form a „core uncoating module“ which helps to generate the mechanical forces needed for viral uncoating.

The VirX consortium builds on these findings to further explore the importance of this cellular pathway for viral infection. The main goals are to: (i) identify further components of the core module, (ii) establish assays to monitor in vivo the interaction between the ZnF-UBP domain and ubiquitin, and set up screen for molecules interfering with these interactions, (iii) establish mouse models to further analyze the processes involved. Other members of the consortium examine clinical samples or test the importance of the Ubiquitin Proteasome pathway or of other viruses. Importantly, the molecular information gained by these studies is used by mathematicians in the VirX consortium to model the role of the uncoating module and relate it to the observed in vivo effects.

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A systems biological approach to the anti-atherogenicity of high-density lipoproteins

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Low blood levels of HDL-cholesterol increase the risk of coronary heart disease (CHD). HDL particles are complex macromolecules containing hundreds of lipid species and dozens of proteins and exerting many potentially anti-atherogenic activities. Pathological conditions cause quantitative and qualitative molecular changes in HDL components and, thereby, dysfunction. To identify structure-function-disease relationships of HDL we isolated HDL particles from the plasma of 25 healthy subjects and 41 patients with CHD. We characterized their protein and lipid abundances by mass spectrometry as well as their biological functionality towards cells relevant for the pathogenesis of CHD, namely the ability to induce cholesterol efflux from macrophages, to inhibit the apoptosis of endothelial cells and to promote the phosphorylation of endothelial nitric oxide synthase. The data on clinical and anthropometric features of the patients, the protein and lipid composition as well as functionality of HDL are integrated to identify components and functions which differentiate HDL of patients and controls. The best discriminators of disease status as well as function and dysfunction of HDL will be followed-up by targeted validation studies to unravel their clinical utility as biomarkers for the diagnosis and personalized management of individuals at increased risks of CHD.

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