MONDAY, OCTOBER 29 2018

02:00 PM – 03:30 PM

Developmental Systems Biology - DEV

Metabolic activity within Escherichia coli macrocolonies and biofilms

Xiang Zhou[1], Wataru Shoji[2], Martin Robert[* 2, 3] on behalf of Martin Robert
[1]Advanced Molecular Chemistry Course, Department of Chemistry, Faculty of Science, [2]Frontier Research Institute for Interdisciplinary Sciences, [3]Institute for Excellence in Higher Education, Tohoku University, Sendai, Japan

Secondary topic : Quantitative Systems Physiology
Your abstract : *Escherichia coli (E. coli)* is often considered as a unicellular organism but it can also form complex multicellular structures such as macrocolonies and biofilms. Some forms of differential physiological function have previously been observed in such bacterial structures, but little is known about the associated metabolic activity. To explore the metabolic phenotype of *E. coli* within complex colony spaciotemporal patterns we use a series of metabolic genes fused to Venus Yellow Fluorescent Protein (YFP). This allows to visualize the expression of several central carbon metabolic enzymes and regulators during the development of large colony structures under various nutritional conditions. Current results show that while gene expression patterns are often similar across strains and appear correlated with cell density within the colonies, we also observe interesting variations in both the level of expression and localization of some metabolic enzymes and regulators around the colony periphery and emerging internal structures. Moreover, changes in environmental conditions affect both the colony structures and the expression level of several enzymes. Our results provide some insight into the partitioning of metabolic activity within developing macrocolonies and biofilms.

Disclosure of Interest: None Declared

Comparative biophysics of the mitotic spindle in nematode embryos

Marie Delattre[*1], Thibault Brugière[1]
[1]LBMC, CNRS ENS Lyon, Lyon, France

Your abstract : The cell is a level of biological organisation that has been poorly explored from an evolutionary perspective because basic cell functions (e.g. cell division) show remarkable conservation across phyla. Thus, an essential question remains: to what extent cellular mechanisms evolve without altering the basic function they sustain?
We have developed the asymmetric cell division of nematode embryos as a study system. The first embryonic division of the nematode *C. elegans* gives rise to two daughter cells of asymmetric size and fate, due to the asymmetric positioning of the mitotic spindle. This initial event is crucial to embryogenesis and conserved in most nematode species. We characterized the intra and inter-species variation in spindle movements in embryos of 42 closely related species of nematodes. We found that significantly different combinations of spindle movements ultimately lead to an asymmetric displacement of the spindle and established that even between virtually identical phenotypes, mechanical optimization of the spindle differs. We are struck by the apparent paradox that an essential cellular function (asymmetric cell division) is maintained over the course of evolution while the underlying mechanisms that sustain it (asymmetric spindle positioning) change rapidly.

We are now exploring which changes to spindle positioning mechanisms have occurred over the course of nematode evolution using comparative biophysics and molecular genetics. This will allow us to identify physical and molecular parameters that are either constraining change or building in flexibility and innovation between nematode species.

Disclosure of Interest: None Declared

A mechanochemical model for the organization of contractions and fluid flows in Physarum polycephalum

Jean-Daniel Julien[* 1], Karen Alim[1]
[1]Biological Physics and Morphogenesis, MAX PLANCK INSTITUTE FOR DYNAMICS AND SELF-ORGANIZATION, Goettingen, Germany

Secondary topic : Developmental Systems Biology

Your abstract : Cytoplasmic streaming, the active transport of the fluid contained in a cell, is observed in very diverse organisms. It is involved in fundamental physiological functions, such as growth, migration, or long-range distribution of molecules.
One example of cytoplasmic streaming is the periodic shuttle flow found in the plasmodium of slime moulds. These single-celled organisms form networks of tubes. Periodic streaming of the cytoplasm takes place inside these tubes, driven by the mechanical contraction of the acto-myosin network wrapping them.
Previous models for the organization of these mechanical waves rely on the diffusion of tension-activating molecules in the peripheral layer of the tube. However, plasmodia are able to grow to almost arbitrary sizes, and the remarkable coherence of cytoplasmic flows, even for large individuals, seems incompatible with simple diffusion.
I will present a mechanochemical model of a contracting tube, coupled to a contraction-regulating molecule advected in the cytoplasm. The model generates patterns of contraction waves and oscillatory flows. Surprisingly, simulated patterns can extend beyond the intrinsic length scale of the model instability. Although long-range patterns appear randomly at first, they can be robustly generated in a growing system.

Disclosure of Interest: None Declared

Delayed bone formation partly explains tibial anterolateral bowing associated with neurofibromatosis type 1

Majid Nazemi[*1], Liesbet Geris[1,2]
[1]University of Liege, Liege, [2]KU Leuven, Leuven, Belgium

Your abstract :
Background: Anterolateral bowing of tibia is observed at birth within 4% of the children diagnosed with neurofibromatosis type 1 (NF-1). Tibial bowing could further increase with growth, leading to spontaneous fracture, nonunion, and amputation in severe cases. NF-1 has been shown to influence cellular interactions involved in angiogenesis and bone formation. In this study, we seek to develop a valid mechanobiological model of early long bone growth to investigate the role of NF-1 relevant delayed bone formation in tibial anterolateral bowing at birth.
Methods: An in-silico model of the fetal tibia was constructed using existing experimental data. Distribution of growth strain was calculated in the model as a function of chondrocyte proliferation and hypertrophy, which are regulated in turn by mechanical stress and concentrations of parathyroid hormone-related peptide (PTHrP) and Indian hedgehog (Ihh). Spatiotemporal distributions of PTHrP and Ihh concentrations were calculated from relevant reaction-diffusion equations, whereas mechanical stress was calculated using poroelastic analysis of the growing tibial model, both implement in the finite element analysis software FreeFem++. The change of the tibial shape during growth was predicted using equations of thermoelasticity, while treating the obtained spatiotemporal distribution of growth strain as thermal strain. Dynamic mechanical loads representing contact pressure at the medial/lateral plateaus were applied to the growing model from 90 days of prenatal life onwards. Angiogenesis and bone formation was assumed to occur when a certain threshold of vascular endothelial growth factor (VEGF) concentration was reached. In order to numerically investigate delayed bone formation, tibial shape at birth was predicted for different thresholds of VEGF.
Results: Our model predictions of longitudinal growth rate and spatial arrangement of proliferative and hypertrophic cells in the epiphysis and diaphysis fit well with physiological observations of the growing tibia. This is indicative of our model reliability in terms of predicting tibial shape during growth. Our results show increased bowing at birth with higher thresholds of VEGF.
Conclusion: NF-1 related delayed bone formation may explain anterolateral bowing of tibia at birth. More sophisticated models accounting for accurate cellular interactions involved in angiogenesis and bone formation are, however, required to further elucidate the underlying mechanisms.

Disclosure of Interest: None Declared

Convolutional neural network-based instance segmentation algorithm to acquire quantitative criteria of early mouse development

Yuta Tokuoka[*1], Takahiro Yamada[1], Noriko Hiroi[2], Tetsuya Kobayashi[3], Kazuo Yamagata[4], Akira Funahashi[1]

[1]Graduate School of Science and Technology, Keio University, Yokohama, [2]Faculty of Pharmaceutical Sciences, Sanyo-onoda City University, Yamaguchi, [3]Institute of Industrial Science, The University of Tokyo, Tokyo, [4]Faculty of Biology-Oriented Science and Technology, Kindai University, Wakayama, Japan

Secondary topic : Methodological developments for Systems Biology

Your abstract : Multicellular organisms develop from fertilized eggs through a number of cell divisions. In development, cell division patterns follow specific rules, although some fluctuations of this pattern are allowed. To uncover the robust mechanisms of development, cell positions in each embryo must be analyzed quantitatively. In embryology, a number of studies have attempted to acquire the quantitative criteria from time-series three-dimensional microscopic images by using image processing algorithms such as segmentation. When used to segment cells or intracellular organelles, several current deep learning techniques outperform traditional image processing algorithms. However, deep learning based segmentation algorithms still have problems, especially in bioimage processing. The most critical issue is that the existing algorithms can perform only semantic segmentation, which distinguishes whether a pixel is within an object (for example, cell nucleus) or not.

In this study, we implemented a novel segmentation algorithm, based on Convolutional Neural Network (CNN) of deep learning methodology, which segments each cell nucleus and adds different labels to the detected objects. This segmentation algorithm is called instance segmentation. Our instance segmentation algorithm, implemented as a neural network, which we named Quantitative Criterion Acquisition Network (QCA Net), substantially outperformed 3D U-Net, which is the best semantic segmentation algorithm based on CNN. QCA Net has a simple structure, combining conventional semantic segmentation algorithms, and can be easily applied to bioimage analysis. We trained QCA Net using part of a single early-stage mouse embryo and performed instance segmentation for time-series images of 11 mouse embryos. We accurately acquired the shape of the nucleus without nuclear region fusion and extracted quantitative criteria of mouse development (such as time-series data for the nuclear number, volume, surface area, and center of gravity coordinates). QCA Net did not only perform nuclear segmentation accurately but also excluded the nuclei of polar bodies, which are difficult to distinguish from cell nuclei in image processing. We consider that QCA Net can significantly contribute to bioimage segmentation in embryology and to generating quantitative criteria from segmented images. Such criteria are needed to uncover the robust mechanisms of embryonic development.

Disclosure of Interest: None Declared

Exploring pancreatic and hepatic cell fate decisions during embryonic development in a systems biological approach

Uwe Benary[*1], David Willnow[2,3], Francesca M. Spagnoli[2,3], Jana Wolf[1]
[1]Mathematical Modelling of Cellular Processes, Max Delbrück Center for Molecular Medicine in the Helmholtz Association, Berlin, Germany, [2]Centre for Stem Cells & Regenerative Medicine, King's College London, London, United Kingdom, [3]Cellular and Molecular Basis of Embryonic Development, Max Delbrück Center for Molecular Medicine in the Helmholtz Association, Berlin, Germany

Secondary topic : Modelling Networks and Circuits

Your abstract : A fundamental understanding of the cellular processes of liver and pancreas development is important because it would help researchers and clinicians to develop novel regenerative therapies for yet incurable diseases of these organs such as diabetes and chronic hepatitis. Liver (Prox1+/Pdx1-) and pancreas cells (Prox1+/Pdx1+) originate from a common region of the foregut but it is still unknown whether they do or do not share a common progenitor cell population. In a systems biological approach we used mathematical models in combination with experimental data that quantifies Prox1+/Pdx1- cells and Prox1+/Pdx1+ cells to test different possible mechanisms of cell fate determination. Our results suggest that the final cell fate is less determined because of a certain degree of plasticity between the cell populations. This may indicate the existence of a cellular mechanism to convert liver and pancreas cells by a yet to be identified mechanism of dedifferentiation and redifferentiation.

Disclosure of Interest: None Declared

Role of OCT4 in establishing and maintaining chromatin architecture during stem cell self-renewal

Subashika Govindan[*1] on behalf of Prof.David Suter, David Suter[1]
[1]Bioengineering, EPFL, Lausanne, Switzerland

Secondary topic : Multi-omics

Your abstract : Chromatin architectural features are key in governing cell type-specific gene expression programs. During mitosis (M), chromatin accessibility and promoter enhancer contacts are disrupted and gene transcription strongly decreases. After mitosis, these chromatin architectural features are re-established to initiate and sustain cell type specific gene expression. While pioneer transcription factors are known to play a crucial role in mediating cell type specific chromatin architecture, their role in re-establishing promoter-enhancer contacts at the M-G1 is unclear.

In ES cells, the pioneer transcription factor OCT4 is indispensable in mediating promoter-enhancer contacts and accessibility of a set of pluripotency-associated regions. We thus hypothesized that OCT4 could also be essential for re-establishing these chromatin architectural features after mitosis. Supporting our hypothesis, we have recent evidence that the absence of OCT4 during M-G1 transition affects the re-establishment of chromatin accessibility of a set of regions throughout the cell cycle. These regions are typically enriched with OCT4 cognate binding sites, suggesting that OCT4 occupancy at the M-G1 transition is crucial for re-establishing accessibility of these regions. We are now aiming to determine whether OCT4 occupancy also plays a role in maintaining chromatin accessibility in later cell cycle stages. To do so, we are now developing an inducible degradation approach to acutely degrade OCT4 for 2 hours at different cell cycle phases. We will also use this method to determine whether OCT4 occupancy is crucial for re-establishment and maintenance of OCT4-associated promoter-enhancer contacts known to regulate expression of pluripotency associated genes.

Disclosure of Interest: None Declared

Modelling protein turnover in developing tomato fruit

Sophie Colombié[*1], Isma Belouah[1], Christine Nazaret[2], Bertrand Beauvoit[1,3], Sylvain Prigent[1], Pierre Pétriacq[4], Alisandra Denton[5], Bjorn Usadel[5], Mélisande Blein-Nicolas[6], Michel Zivy[6], Yves Gibon[1]

[1]UMR 1332 , INRA, Bordeaux, [2]IMB, ENSTBB, Bordeaux INP, 33400 Talence, [3]Univ. Bordeaux, F-33076 Bordeaux Cedex, [4]INRA, Bordeaux, France, [5]RWTH Aachen University, 52074 Aachen, Germany, [6]PAPPSO, GQE, 91190 Gif-sur-Yvette, France

Secondary topic : Multi-omics

Your abstract : Protein turnover, resulting from synthesis and degradation, is an essential process regulating the cellular protein status in cells. Thus, it is crucial to estimate protein stability. Although protein synthesis, and mostly degradation, are generally determined by labelling experiments, this technique is poorly appropriated for growing tissues such as tomato (*Solanum lycopersicum*) fruit. So, we used a simple mathematical model to estimate synthesis and degradation rates of more than a thousand proteins from proteins and transcripts expressed in absolute quantification during tomato fruit development. Proteomic by label-free LC-MS/MS (PAPPSO, http://pappso.inra.fr/) and RNAseq were performed on samples of tomato fruit pericarp harvested at nine stages of development. Protein quantification was obtained from ion intensities (XIC) and absolute quantification of transcripts was enabled by adding spikes in the experimental RNAseq design (Genotoul GeT, Toulouse and Usadel'lab). For the 2,490 transcript-protein pairs, mRNA and protein abundances were poorly correlated and the coefficient of correlation decreased along fruit development and ripening, with transcript abundances decreasing more than protein abundances. Subsequently, a simple Ordinary Differential Equation (ODE) was used to describe the rate of change of protein pool over time as the balance between the rates of protein synthesis and degradation. A least square method allowed to estimate synthesis (*ks*) and degradation (*kd*) rate constants. Theses estimations, confidently performed for 1247 transcript-protein pairs, indicates that 2'30'' were required for the synthesis of a protein while its lifetime was 11 days (median values). We then validated these constants and searched for biological relevance. We thus confirmed that both synthesis and degradation constant values were within the range of the values found for other biological systems, *i.e.* in Arabidopsis and barley for degradation, and in human cells and yeast for both rate constants. We also showed that the primary sequence seemed to poorly influence both rate constants suggesting that each protein harboured an additional level of regulation that was independent of its amino acid sequence. Therefore, we conclude that absolute quantification of omics is crucial and very useful to perform modelling and assess turnover rate of proteins.

Disclosure of Interest: None Declared

Exploring cell cycle gene regulatory network dynamics through the algebraic analysis of its structural reachability properties

Eduardo CHAIREZ-VELOZ[1], Elizabeth ORTIZ-GUTIÉRREZ[2], José Luis CALDÚ-PRIMO[3], Elena R ALVAREZ-BUYLLA[4], Juan Carlos MARTINEZ GARCIA[* 1] on behalf of Eduardo Chairez-Veloz; Elizabeth Ortiz-Gutiérrez; José Luis Caldú-Primo; Elena R Álvarez-Buylla; Juan Carlos Martínez-García

[1]Automatic Control Department, Cinvestav-IPN, [2]Departamento de Ciencias Naturales, UAM-CUAJIMALPA, [3]Phd Program in Biomedical Science, [4]Instituto de Ecología & Centro de Ciencias de la Complejidad, UNAM, MEXICO CITY, Mexico

Secondary topic : Multiscale Systems Biology

Your abstract : The spatio-temporal regulation of cell cycle (CC) in multicellular organisms is essential during the morphogenetic process since it relies on the coordinated progression of cell cycle and its variations, *i.e.* , CC arrest, reactivation, which together with endoreduplication, and cell growth are important in the emergence of morphogenetic patterns. Its experimentally grounded regulatory interactions that interlink these processes can be integrated into a modularly structured Gene Regulatory Network (GRN) and mathematically described through discrete Boolean models. Some low-dimensional Boolean GRNs have been proposed to recover the cyclic gene activation configurations observed in different CC stages, and they have been validated via robustness and mutant analysis. In spite of the recent interest and advances in CC-GRNs models, systematic analysis that elucidate the role of individual genes when perturbated by combinatorial switched-on and off actions, implicated in disrupting the cyclic behaviour, are still very scarce. Following this idea, we put forward an analytical procedure which harnesses the structural reachability properties of Boolean GRNs in its algebraic form, obtained via Semi-Tensor Product approach (STP). As a concrete study case, we used the Boolean GRN model that recovers the cyclic behaviour of *Arabidopsis thaliana* CC. Our findings suggest that their molecular components acquire a novel potentiality when are temporally switched-on and off throughout the CC progression, not only in the Boolean GRN, but also in the approximated continuous model. For example, we found that suitable time-manipulations by external control input in genes such as APC/C and MYB3R1/4 induce endoreduplication and provoke cell cycle arrest, respectively. We concluded that the reachability analysis can give us insights about how developmental, physiological or enviromental cues could be acting on individual genes to coordinate CC network dynamics with the spatio-temporal CC regulation.

Disclosure of Interest: None Declared

Evolutionary and Ecological Systems Biology - EVO

Determinants of protein evolutionary rate in multicellular organisms

Dinara Usmanova[*1], German Plata[1], Dennis Vitkup[1]
[1]Systems Biology, Columbia University, New York, United States

Secondary topic : Multiscale Systems Biology

Your abstract : Protein evolutionary rates are one of the fundamental parameters of molecular evolution. Gene expression has been shown to consistently and strongly anti-correlate with evolutionary rates across multiple species. However, in multicellular organisms, different tissues and cell types have different mRNA expression levels and protein abundances, and it is not yet clear how the combined contributions from such disparate expression profiles influence protein evolutionary rates. In agreement with previous observations we showed that in animals the strongest anti-correlation between expression and evolutionary rate occurs in neural tissues. Moreover, analyzing single-cell transcriptome data from the mouse brain we demonstrated that expression levels in several specific neuron types, such as excitatory cortical and hippocampus neurons, can explain up to ~25% of the variance in protein evolutionary rates across entire mammalian proteomes. Interestingly, in all studied animals neural tissues are almost solely responsible for controlling evolutionary rates, whereas expression in non-neural tissues make only a minor independent contribution, explaining only an additional 1-2% of variance. In contrast to animals, in plant species we observed cases in which several specific tissues, for example flowers and roots in *Arabidopsis*, play a predominant role in constraining the evolution of proteins. Furthermore, gene ontology enrichment analyses suggest that the energetic demands of synaptic transmission in the animal brain, and processes related to cell wall biosynthesis in growing plant tissues create stringent constraints in the corresponding cell types, making them dominant in defining molecular evolution for the whole organism. This work provides a fascinating and previously unexplored connection between tissue functions, metabolism, and protein evolution.

Disclosure of Interest: None Declared

The problems of transport of substances through the cell membrane at the early stages of evolution from the point of view of system biology

Evgenii Zafirov[*1], Alexei Melkikh [1], Maria Sutormina[1]
[1]Institute of Physics and Technology, URAL FEDERAL UNIVERSITY NAMED AFTER THE FIRST PRESIDENT OF RUSSIA B.N.YELTSIN, Ekaterinburg, Russia

Secondary topic : Systems Biology for Synthetic Biology

Your abstract : The issue of cell survival at the early stages of evolution under changing external conditions has not yet been solved and seems to be relevant for understanding evolutional processes. On the one hand, the early cells had to be as stable as possible to changes in the external environment, on the other hand, the restriction of resources should also be taken into account.

An algorithm for determining the dependence of the control on the external ion concentration providing a maximum efficiency is developed, while limiting the internal concentration of ions at the same time for the simplest system in which one substance is transferred by two active transport systems. The purpose of the calculations is to check the possibility of simultaneous availability of the properties of efficiency and the ability to maintain the internal environment constant (homeostasis) for living systems. This also applies to the system of transport of substances in the simplest cells.

Models of transport of substances in different types of cells, presented earlier [1-2] were used in the calculations. These models allow obtaining dependences of internal concentrations and rest potential on external concentrations. The equation for efficiency (for the case of two active transport systems) was used and transformed to evaluate the efficiency of transport systems. This equation was introduced earlier [1].

It is revealed that, *u (control)* is the only controlling parameter, both for efficiency and for homeostasis. This parameter takes into account the speed (power) of the operation of active transport systems carrying one type of substance relative to each other. Earlier [2] it was assumed that the value of *u* depends on the concentrations in a power-law manner. The developed algorithm for finding the extremum is aimed at obtaining a dependence of *u* on the external concentration, for each point of which the internal concentration is in the admissible interval, and the efficiency is the maximum possible.

The results of this research are important for understanding the evolution processes at the early stages, as well as for modeling the hypothetical cell named Last Universal Common Ancestor.

The reported study was funded by RFBR according to the research project № 18-51-05007 arm_a.

1. A. V. Melkikh and M. I. Sutormina, *Developing Synthetic Transport Systems* (Springer Science + Business Media Dordrecht, 2013) 199 p.
2. A. V. Melkikh and V. D. Seleznev, Orig. Life Evol. Biosph. **38**, 343-353 (2008).

Disclosure of Interest: None Declared

Host genotype shapes the assembly of both the gut microbiota and the surrounding bacterioplankton in the freshwater crustacean Daphnia magna

Ellen Decaestecker[*1], Emilie Macke[1]
[1]KU LEUVEN, Kortrijk, Belgium

Your abstract : In spite of the growing interest into the role of gut microbiota in host physiology and health, the mechanisms governing its assembly are poorly understood. The gut microbiota is increasingly recognized to contribute to a wider metacommunity maintained by dispersal between host-associated and free-living microbial communities, and shaped by within-host sorting processes. Understanding gut microbiota assembly thus requires to consider deterministic and stochastic processes occurring across multiple scales. Combining metabarcoding with gut microbiota transplants, we here show that in the freshwater crustacean *Daphnia magna*, host genotype and diet interact to shape the structure of both the gut microbiota and the surrounding bacterioplankton. When different *Daphnia* genotypes were exposed to identical microbial communities, both the gut microbiota and the bacterioplankton diverged to reached a genotype- and diet- dependent taxonomic composition. Exposure of germ-free *Daphnia* to different microbial inocula further revealed an effect of the external microbial source on the gut microbiota structure. Overall, the taxonomic composition of the gut microbiota was however very different from that of the bacterioplankton, and was characterized by a lower alpha diversity, suggesting a selective, genotype-dependent, recruitment of gut symbionts in this species. Together, these results indicate strong reciprocal interactions between *Daphnia*, their gut microbiota and the bacterioplankton, and provide evidence that *Daphnia* mediate the assembly of their associated microbial communities, both within their gut and in their close environment, depending on their genetic background. This study also illustrates the impact of evolution (i.e. genetics) on ecological processes (i.e. community assembly), providing strong support to eco-evolutionary dynamics theory.

Disclosure of Interest: None Declared

In silico experimental evolution shows that complexity can rise even in simple environments

Guillaume Beslon[*1], Vincent Liard[1], David Parsons[2], Jonathan Rouzaud-Cornabas[1]
[1]INSA-LYON, [2]INRIA, Villeurbanne, France

Your abstract : Systems biology is often viewed as reverse engineering of biological systems. However, contrary to reverse engineering, systems biology deals with objects that have not been designed, that have no given purpose and that don't follow engineering rules (e.g. modularity, standardization…). Indeed, we don't know what are the "design rules" that evolution imposes to biological systems while this knowledge would be a valuable interpretative framework for systems biology.

One of the recurrent questions on that matter is the origin of the striking molecular complexity of biological systems. Answering this question requires deciphering the complex interactions between all the forces that drive evolution, including selective and non-selective ones. In this context, simulation is a valuable tool as it enables to observe how organisms grow in complexity (or not) when they evolve in environments which complexity is perfectly mastered. In Liard et al., 2018, we used the Aevol platform (www.aevol.fr), to design an in silico experiment in which populations of organisms evolved in an environment designed to enable survival of the simplest possible organism (i.e., an organism whose genome encodes a single gene) and in which this simple organism have the best possible fitness. By repeatedly evolving organisms in this experimental design, we observed two very different outcomes: some lineages were able to quickly find the optimal genotype (one single gene) and were then stable for the rest of the experiment. However, most lineages were not able to find the optimal genotype and showed a very different dynamics with continuous complexification through gene acquisition all along the experiment. Importantly, these "complex" organisms ended up with fitness values typically 10 to 100 times lower than the simple ones.

Our results show that, in such a simple constant environment, there is a decoupling between the molecular complexity of the organisms and the complexity of the environment. This shows that selection for complexity is not mandatory for complexity to evolve and that complex biological structures could flourish in conditions where complexity is not needed. Reciprocally, the global function of complex biological structures could very well be simple. We think this result is greatly significant for both evolutionary biology and systems biology.

Liard, et al. (2018) The Complexity Ratchet: Stronger than selection, weaker than robustness. In: Proceedings of ALife 2018.

Disclosure of Interest: None Declared

The impact of promoter architecture on signal integration in B. subtilis quorum sensing - a combined experimental and computational study

Sarah Kaspar[* 1, 2], Valentina Rippa[2], Stephanie Trauth[2, 3], Diana Wolf[2], Maren Nattermann[2], Ilka Bischofs[2, 3], Jürgen Pahle[1, 2]
[1]BIOMS, [2]BioQuant, Heidelberg, [3]Max Planck Institute for Terrestrial Microbiology, Marburg, Germany

Your abstract : Bacteria use quorum sensing (QS) to estimate their density and to trigger cooperative behaviour in response. In this process, the signals of various QS molecules are often fed into the same gene activation process. For example, in *B. subtilis* the species-specific and the strain-specific signals converge to regulate the master regulator ComA by independently regulating the overall abundance and the phosphorylation status of the transcription factor. Whether and how different QS signals are integrated at the level of gene expression is not well understood.
Here we provide experimental evidence suggesting that promoter architecture is a key factor for signal integration and the decoding of information encoded by different QS signals. We furthermore developed a mathematical model for QS-dependent gene expression composed of two modules: (1) A DNA-binding and (2) a gene expression module. The model reveals promoter features that could be crucial with respect to the weighting between different QS signals. These features might therefore also play an important role in determining the extent of intra- and interstrain cooperative behaviour.

Disclosure of Interest: None Declared

Modelling of functional evolution of electrogenic bacterial communities

Anatoly Sorokin[* 1], Mami Kainuma[2], Lukasz Szydlowski[2], Igor Goryanin[2, 3, 4]
[1]Moscow Institute of Physics and Technology, Dolgoprudy, Russia, [2]Okinawa Institute of Science and Technology, Okinawa, Japan, [3]University of Edinburgh, Edinburgh, United Kingdom, [4]Tianjin Institute of Industrial Biotechnology, Tianjin, China

Secondary topic : Modelling Networks and Circuits

Your abstract : Microbial Fuel Cells (MFC) are emerging technology of energy-efficient wastewater treatment as compared to the commonly applied aerobic methods. MFC is using microbial activity that results in electricity generation in the process of consumption of biomaterials. The overall efficiency of MFCs is due to the activity of mature microbial consortia that reach optimum performance over time. Our aim is to understand the behaviour of the microbial community in the electrogenic environment. To achieve this, we have developed flux model of the biochemical processes taking part in the community and analyze its metabolic abilities. We compare predictions of the model with results of the metagenomic analysis of the electrogenic community evolving under various external voltage conditions.

Disclosure of Interest: None Declared

Modelling the chemical defensome networks - a comparative dynamic visualisation of the involved genes and interactions in two fish species and humans

Marta Eide[*1], Xiaokang Zhang[2], Odd André Karlsen[1], Eileen Marie Hanna[2], Nello Blaser[3], Pål Puntervoll[4], Inge Jonassen[2], Anders Goksøyr[1]
[1]Department of Biological Sciences, [2]Computational Biology Unit, Department of Informatics, [3]Department of Mathematics, University of Bergen, [4]Centre for Applied Biotechnology, Uni Research Environment, Bergen, Norway

Secondary topic : Modelling Networks and Circuits

Your abstract : Introduction: The chemical defensome comprises an integrated network of gene families and pathways that together function to metabolize and eliminate harmful compounds. It is critical for survival and highly conserved from invertebrates to fish and mammals. But the chemical defense genes of Atlantic cod (*Gadus morhua*), a commercially and ecologically important species, are poorly studied. The object of this investigation is to look into the chemical defensome network of cod and compare it with those in zebrafish (*Danio rerio*) and human (*Homo sapiens*).
Methods: Based on available literature on genes involved in the chemical defensome, we searched the zebrafish and human genomes, as well as the newly curated Atlantic cod genome assembly, to identify the genes comprising the defensome networks. Furthermore, by using the protein-protein interactions covered by the STRING database, we modeled the complex networks of genes and interactions involved in the chemical defense responses and visualized them in Cytoscape.
Results and discussion: The modelling of fish and human chemical defensomes enables a dynamic visualization of these complex networks. Furthermore, graph theory methods can be used to study relations and processes within the network in a comparative manner. For instance, the species-specific networks indicate a different number of interactions between the separate phases of biotransformation in human and zebrafish, which can indicate differently evolved signaling pathways.

The study is part of “dCod 1.0: decoding systems toxicology of cod (*Gadus morhua*) – environmental genomics for ecosystem quality and risk assessment”, part of Centre for Digital Life Norway, (project no. 248840) and "iCod 2.0: Integrative environmental genomics of Atlantic cod (*Gadus morhua*)” (project no.244564/E40), funded by the Research Council of Norway and the University of Bergen.

Disclosure of Interest: None Declared

Microbial ecology of reticulation networks under conditions of intermittent water supply

Tobi Louw[*1]
[1]Process Engineering, Stellenbosch University, Stellenbosch, South Africa

Secondary topic : Multiscale Systems Biology

Your abstract : Intermittent water supply is prevalent in many underserved communities globally. While links between adverse health effects and intermittent water supply has been established in certain cases, other studies assert that intermittent water supply does not significantly affect public health. This apparent ambiguity can be attributed to the limited understanding of microbial ecological systems in reticulation networks subjected to intermittent water supply. Furthermore, the potential for the development of antimicrobial resistance in high bacterial load environments should not be underestimated. Agent Based Modelling provides a unique approach to investigate microbial interactions in systems subjected to changes in environmental conditions.

The intermittent water supply system microbiome will be influenced by the cycle between high-shear, anoxic and no-shear, aerobic conditions. This study uses an Agent Based Modelling approach to assess the interactions between various classes of microbes under fluctuating environmental conditions. The modelling frameworks provided by the International Water Association's Activated Sludge Model 3 as well as Anaerobic Digestion Model 1 are used to provide a first approximation of growth models and parameters.

The results of the study are used to identify critical conditions leading to exceptionally high bacterial loads which may lead to waterborne disease as well as the development of antimicrobial resistance. Conversely, supply protocols which minimize bacterial loads are also identified. The modelling approach can serve to inform governing bodies on the safe provision of water when intermittent supply is unavoidable.

Disclosure of Interest: None Declared

Methodological developments for Systems Biology - METH

Status report: parameter estimation of a large-scale mechanistic model for mast cells in asthma

Thomas Ligon[*] [1], Irina Balaur[2], Alexander Mazein[2], Diane Lefaudeaux[2], Charles Auffray[2], Leonard Schmiester[3, 4], Jan Hasenauer[3, 4]

[1]Faculty of Physics and Center for NanoScience (CeNS), LUDWIG-MAXIMILIANS UNIVERSITÄT MÜNCHEN, Muenchen, Germany, [2]European Institute for Systems Biology and Medicine, Université de Lyon, Lyon, France, [3]Institute of Computational Biology, Helmholtz Zentrum München-German Research Center for Environmental Health, Neuherberg, [4]Center for Mathematics, Technische Universität München, Garching, Germany

Secondary topic : Modelling Networks and Circuits

Your abstract : Asthma is a complex disease involving various mechanisms. A deeper understanding of the mechanisms of asthma is needed for better diagnosis and therapy. To this end, the development of a mechanistic description of asthma was initiated, the AsthmaMap (http://disease-maps.org/projects/asthma, Mazein et al. (2016) ERS LSC). Our current work employs the AsthmaMap to build a mechanistic model of mast cell dynamics, with the goal of improving our understanding of the disease and offering a tool for predicting the efficacy of medications. We began by deriving a Systems Biology Markup Language (SBML) model from the mast cell part of the AsthmaMap and additional literature. For the simulation and parameter estimation of the SBML model, we used the toolboxes AMICI (Fröhlich et al., 2017, PMID 28114351) and PESTO (Stapor et al., 2018, PMID 29069312). Quantitative experimental data were extracted from several published studies (e.g., Parravicini et al., 2002, PMID 12089510). We obtained an SBML model with CellDesigner markup for mast cell signaling, which has more than 300 species and 500 parameters, and includes kinetic laws for all reactions. Additionally, we used a workflow adapted from a large cancer project, enabling easier exchange of data between various sources and use of it on multiple machines. This work demonstrates that the parameter estimation of the model is challenging, due to nonlinear dynamics, and many of the published data sets could only be applied after the model was enhanced. However, the current model already captures several aspects of the mast cell response to allergens. Our study has shown that the translation of a disease map to a mechanistic computational model is a complex process involving a series of steps, among others the establishment of a repository of quantitative experimental data. In the future, this repository might be built alongside the disease map. Overall, we have made substantial progress towards the development of a predictive model for mast cell dynamics.

Disclosure of Interest: None Declared

System-level gene expression profiling by gene expression commons for RNA-seq

Jun Seita[* 1, 2, 3], Hiroki Sugishita[2], Eiryo Kawakami[1], Tarzo Ohta[4]
[1]Medical Sciences Innovation Hub Program, [2]Center for Integrative Medical Sciences, RIKEN, Yokohama, [3]Center for Advanced Intelligence Project, RIKEN, Tokyo, [4]Database Center for Life Science, Joint Support-Center for Data Science Research, Research Organization of Information and Systems, Chiba, Japan

Secondary topic : Multi-omics

Your abstract : Each gene has a different dynamic-range of its expression. Biological significance is different between 1000 FPKM in gene A and in gene B, or 2-fold change in gene X and in gene Y. For system-level understanding of gene expression, it is necessary to know dynamic-range of each gene expression.
To achieve this, we collected 100k mouse RNA-seq data and 50k human RNA-seq data from public repositories, then mapped, counted, and statistically analyzed to obtain gene expression dynamic-ranges. The results are integrated into Gene Expression Commons for RNA-seq where user's RNA-seq data is mapped onto dynamic-range reference.
Gene Expression Commons has been open platform for microarray based objective gene expression profiling using same strategy. 4000 scientists from over 60 countries have been submitted gene expression data of 3500 cell types. They have generated 2000 working models, and resulted over 100 publications. We aim to provide same open platform for RNA-seq via Gene Expression Commons for RNA-seq (https://gexc.riken.jp).

Disclosure of Interest: None Declared

Toward a scalable multiscale analysis of biomolecular data

Susanne Gerber[1], Illia Horenko[* 2]
[1]Faculty of Biology, Johannes Gutenberg University Mainz, Mainz, Germany, [2]Faculty of Informatics, Universita della svizzera italiana, Lugano, Switzerland

Secondary topic : Multiscale Systems Biology

Your abstract : Being based on the exact law of a total probability, Bayesian and Markov models - at least in principle - allow model-error-free insights into dynamics of complex systems. During the recent decades these models became broadly recognised as a central instrument in a wide range of applied sciences. For example, in a network science, the inferred Markovian invariant measure gives a ranking of the nodes in underlying graphs, as in the Google PageRank algorithm.In biophysical molecular dynamics (MD), Markov State Models inferred from the MD time series data provide equilibrium probabilities for molecular conformations and are used as main instruments in computations of various dynamical characteristics, including the metastable states, most probable reaction pathways and in comparison with experimental data.

However, application of common Markov tools to realistic biomolecular data (like MD trajectories) can be seriously biased or even prohibited due to the latent impacts from unobserved scales, by very low signal-to-noise ratios as well as due to the relatively small statistics sizes that are combined with huge phase space dimensions - and leading to the unfeasible model uncertainties and exploding numerical cost. Several recent methodological developments aiming at a joint treatment for these problems will be presented. Applications of introduced methods will be exemplified on: (i) toy model systems, (ii) on analysis of MD data for a Parkinson-relevant alpha-synuclein molecule, and (iii) on analysis of single cell human mRNA data.

Disclosure of Interest: None Declared

In search for optimal parameters in three-compartmental model of cholesterol homeostasis

Magdalena Żulpo[1] on behalf of Krystian Kubica, Joanna Balbus[2] on behalf of Krystian Kubica, Krystian Kubica[*1] on behalf of Krystian Kubica
[1]Department of Biomedical Engineering, [2]Department of Pure and Applied Mathematics, WROCLAW UNIVERSITY OF SCIENCE AND TECHNOLOGY, Wroclaw, Poland

Secondary topic : Quantitative Systems Physiology

Your abstract : The analysis of the two-compartment model of cholesterol homeostasis has shown a significant influence of the amount of cholesterol carried by the bile on the total cholesterol concentration in the second compartment, i.e. peripheral blood. To study the influence of bile circulation on the cholesterol homeostasis, we have developed a three-compartment model by the addition of a new compartment, describing changes of the bile amount in the gallbladder. Now our model allows to consider: cholesterol synthesis in the liver, cholesterol exchange kinetics between compartments, the rate of cholesterol entry and loss with bile, the loss of cholesterol due to the conversion into cholic acid, cholesterol consumption by tissues, dietary cholesterol, gallbladder filling and emptying rates and gallbladder bile accumulation ability. Our model consists of three equations (ODE) and fourteen parameters. All parameters in our model can be divided into five groups:

a) parameters whose values result directly from physiological knowledge:
the tissues' demand for cholesterol, volume of blood serum in the liver and in the blood stream, total amount of bile, loss of cholesterol with feces, time of gallbladder filling and emptying,

b) parameters whose values result indirectly from physiological knowledge through equations describing particular processes. This group includes: parameter describing the rate of cholesterol synthesis, parameters responsible for the rate of cholic acid synthesis and the medium rate of cholic acid flow from the liver into the gallbladder,

c) parameters which are bound together by postulated equations to describe known physiological changes,

d) parameters estimated on the basis of a case study,

e) parameters which could be described as effective rate constants responsible for multistep processes of cholesterol exchange between two compartments: blood in the liver and peripheral blood.

Based on the set of already estimated initial values of parameters and range of their changes we can search for their optimal values to get the best fit to the case study results. The process of optimization should comply with the principle that the known processes associated with cholesterol homeostasis take place according to physiological knowledge. Finally it has to be stressed that values of most parameters may vary between different healthy subjects. However, these should not significantly exceed the estimated volatility ranges.

Disclosure of Interest: None Declared

A model screening framework based on non-linear ODE systems for the generation of calcium oscillations in single neurons

Ravutla SuryaTeja[1], Vaibhav Dhyani[*1], Sarpras Swain[1], Kishalay Mitra[1], Lopamudra Giri[1]
[1]Department of Chemical Engineering, Indian Institute of Technology Hyderabad, Sangareddy, India

Secondary topic : Single-cell Systems Biology

Your abstract : Calcium (Ca^{2+}) spiking in neurons generates versatile intracellular signals that control crucial functions such as synaptic plasticity and synchronicity of cell differentiation and migration. Although there has been a significant effort towards constructing biophysical models for Ca^{2+} oscillations, comparison of simulated results and experimental data remains sparse. Specifically, it remains challenging to estimate the kinetic parameters for these non-linear models generating oscillatory output.

In this work, we propose a computational toolbox that can be used for selection of the biophysical models and estimate the kinetic parameters for single cell Ca^{2+} oscillations using the genetic algorithm (GA). As a proof of concept, the framework has been used for selecting the oscillatory model for hippocampal neurons where fluorescent labeling and confocal imaging were used to measure the Ca^{2+} oscillations. Four different models based on the non-linear ODE systems were tested in the framework for comparison of their output to the experimental observations. First is the Li-Rinzel model for calcium-induced calcium release (CICR) based on the assumption of constant inositol 1,4,5-triphosphate (IP_3) concentration. Second is the G-*ChI* model based on the consideration of the biochemical pathways for IP_3 and the impact of glutamate on the IP_3 cycle. The third is the Lavrentovich-Hemkin model integrated with Ca^{2+} influx via voltage-gated calcium channel (LH-VGCC). The fourth model is an integrated G-*ChI*-VGCC model where both biochemical pathways for IP_3 dynamics and the physiological properties of the VGCC were combined.

Based on the results obtained from the framework it was observed that the robust G-*ChI*-VGCC model was not only able to capture the trend of Ca^{2+} oscillations more accurately but also displayed least RMSE. This can be attributed to the presence of more number of parameters in the model, like the membrane potential, channel activation/inactivation exponents, and the extracellular Ca^{2+} concentration that can be tuned to control the cytosolic Ca^{2+} oscillation. A detailed parametric sensitivity analysis for the selected model was further performed.

The major novelty of the work is to set the workflow that can be successfully used for automated selection of models for Ca^{2+} oscillations in single neurons. Based on the accuracy of experimental data and simulated results it can be stated that the proposed framework can be comprehensively used.

Disclosure of Interest: None Declared

Unravelling the hidden universe of small proteins in bacterial genomes

Samuel Miravet-Verde[*1], Luis Serrano[1], Maria Lluch-Senar[1] and Design of Biological Systems
[1]Design of Biological Systems, CENTRE FOR GENOMIC REGULATION, Barcelona, Spain

Secondary topic : Methodological developments for Systems Biology

Your abstract : Identification of short open reading frames (smORFs) encoding for small proteins (≤100 amino acids; SEPs) is an open challenge in genome annotation and protein discovery fields. In this work, we assessed limitations of experimental SEPs discovery concluding that RNA and protein abundance together to the number of unique tryptic peptides (UTPs) and their responsiveness to mass spectrometry (MS) are limiting factors. Remarkably, using a 'decoy' dataset of SEPs that should not present signal in MS we observed that 1 UTP is not enough to trust the existence of a protein. This condition makes SEPs identification, that tend to have none or few UTPs, a very complex task. To tackle this problem, we developed RanSEPs, a random forest-derived computational approach based on the randomization of biased training sets to predict novel small proteins in bacterial genomes. Predictions were validated and compared to other software tools using a set of actual SEPs detected in 124 MS samples from 6 different Mycoplasma species and *Escherichia coli*, synthetic peptides and SEPs validated on the literature. Our tool ranked as the best methodology for the detection of novel SEPs (AUC=94%) and we demonstrated that it properly predicts every SEP with signal in MS and successfully guides targeted protein discovery. Later, our tool was used to describe 109 bacterial 'smORFomes', the most important species-specific features associated to coding sequences and the fact that up to 25% of proteins in bacteria could be SEPs. In addition, integration of RanSEPs predictions with transcriptomics data from 11 bacterial species showed that some formerly annotated as non-coding RNAs could be encoding for SEPs. Finally, functional studies of SEPs highlighted an enrichment in membrane, translation, metabolism and DNA/RNA binding categories. Interestingly, 9.7% of the SEPs included a secretion signal, indicating that they could participate in quorum sensing and/or signaling. This work represents the first comprehensive annotation of bacterial genomes and provides a tool to unmask the hidden universe of small bacterial proteins.

Disclosure of Interest: None Declared

Improvement of model based design quality constraining kinetic and stoichiometric models during optimization

Egils Stalidzans[*1], Andrus Seiman[2], Karl Peebo[2], Vitalijs Komasilovs[1], Agris Pentjuss[1]
[1]LATVIA UNIVERSITY OF LIFE SCIENCES AND TECHNOLOGIES, Jelgava, Latvia, [2]Center of Food and Fermentation Technologies, Tallinn, Estonia

Secondary topic : Systems Biology for Synthetic Biology

Your abstract : Mathematical models can not take into account all complexity of life. Still, some knowledge can be simplified and taken into account in the form of optimization constraints to improve the feasibility of model-based designs of metabolic pathways in organisms. The irregular applications of different constraints indicate a potential for design feasibility improvement by appropriate application of the constraints. Some constraints (mass balance, energy balance, steady state assumption) serve as a basis for modelling approaches. Some others (total enzyme activity constraint, homeostatic constraint) are proposed decades ago and frequently ignored in design development. Several new approaches of cellular analysis have made possible the application of constraints like cell size, surface, resource balance, etc.

Constraints for kinetic and stoichiometric models can be grouped according to their applicability preconditions in (1) general constraints, (2) organism-level constraints, and (3) experiment-level constraints. General constraints (steady state assumption, mass balance, energy balance and others) are universal and are applicable for any system. Organism-level constraints (homeostatic constraint, total enzyme activity constraint, cytotoxic/unfeasible metabolite concentrations and others) are applicable for biological systems and usually are organism-specific, but thy do not depend on experimental conditions. To apply experimental-level constraints (cellular resources, biomass composition, cell mass, doubling time, cell geometry and others), peculiarities of the organism and the experimental set-up have to be taken into account to calculate the values of constraints.

The application of steady-state constraints in both kinetic and stoichiometric models enables the synergy between two model types. Most kinetic models are relatively small but include kinetic parameters and take into account metabolite concentrations. The steady-state fluxes found in kinetic models can be put into stoichiometric models as constraints to test the feasibility of the kinetic model steady-state flux distribution at genome scale where mass and energy balance can be taken into account at organism level. The range of metabolite concentrations in kinetic models can be also used to calculate lower and upper constraints of reaction fluxes in stoichiometric models where concentrations cannot be directly applied.

Disclosure of Interest: None Declared

Translational modeling of drug efficacy in cancer

Lisa Turnhoff[* 1, 2], Andreas Schuppert[1, 2]
[1]Joint Research Center for Computational Biomedicine, [2]Aachen Institute for Advanced Study in Computational Engineering Science, RWTH Aachen University, Aachen, Germany

Secondary topic : Systems Medicine

Your abstract : Over the last years, great progress has been made in the field of predicting the sensitivity of cancer cell lines towards diverse drug compounds based on their molecular data profiles, complementing the abundance of public cell line data sets of various kinds with tools to systematically analyze and model in vitro drug response. Nevertheless, it remains a challenge to translate the knowledge gained in cell line experiments about mechanisms associated with drug response into a patient-relevant context: a multitude of anti-cancer compounds that seem promising in pre-clinical trials still fail when they are finally applied to patients and up until now, existing translational models that address this issue are rare and highly heterogeneous.

In our study, we comprehensively evaluate modeling descisions of such translational modeling routines aiming at enhancing the overall predictivity. Using the uniFied translatiOnal dRug rESponsE prEdiction platform FORESEE, we systematically explore the impact of each module of the modeling process on the model's performance in order to attain an optimized combinatorial routine. This ranges from transforming the cell line drug response data that provides the outputs for the model training process and preprocessing the molecular cell line data by batch-correcting, filtering and transforming them into predictive input features, over training different types of machine learning models, to predicting and validating the generated model on preprocessed patient data sets.

Moreover, we examine different public gene expression data sets that characterize certain cancer cell types as well as more hybrid alternatives, such as patient-derived xenografts, to determine subgroups that display a particularly informative behaviour with regard to in vivo drug response. By relating patterns observed in these diverse molecular profiles with each other, we identify coherences that can help in the comprehension of clinical drug response and facilitate more sophisticated treatment decisions in the future.

Disclosure of Interest: None Declared

EV genotyping: a web application for Enterovirus genotyping in deep learning

Shu-Hwa Chen[1], Chieh-Hwa Lin[2], Zhe-Ren Hsu[1], Yi-Hsun Lu[1], Chung-Yen Lin[* 1, 1, 1]
[1]INSTITUTE OF INFORMATION SCIENCE, ACADEMIA SINICA, Taipei, [2]INSTITUTE OF POPULATION SCIENCE, NATIONAL HEALTH RESEARCH INSTITUTES, Maoli, Taiwan

Secondary topic : Systems Medicine

Your abstract : The *Enterovirus* (EV) genus (family ***Picornaviridae***) contains twelve species, including *Enterovirus A* to *H* and *J*, and *Rhinovirus A* to *C up to 308 genotypes*. These viruses cause a wide range of diseases in humans and mammals *with similar symptoms at the stage of initial infection. Among them,* EV-71 and D-68 are notable for their etiological roles in epidemics of severe neurological diseases in children. The current approach to identify serotype of EV is using a panel of antibodies against VP1 and other viral proteins. If a novel EV strain emerged from a recombinant event that joined epitopes of different parent strains, the serological phenotype might fail to reflect clinical virulence. Hence, precise and rapid prediagnosis on EV genotype in the early stage is the key to clinical therapy to prevent severe symptom before vaccine and drug available at this moment.

Here we integrated and corrected EV sequences with their serotypes according to virus classification for NCBI GenBank and the International Committee on Virus Taxonomy (ICTV) taxonomy. By using corrected sequences of EV family with their serotype around 48,382 records, we have applied deep learning approach (Convolutional Neural Networks, CNN) to classify these 308 genotypes of EV family. Although the macro-average of prediction accuracy by five folds cross-validation (CV) is around 80%, the micro-average for EV-71 and D-68 are up to 99% and 98% respectively. So here, we composited the pipeline by the filter for homology search (Coverage>80% with E<1.0E-5) and CNN model to ensure the submitted sequences belonged to EV family then classify them into suitable genotype. Here, we implement this approach as EV genotyping and have constructed the web application that is fully automatic to provide precise and rapid prediagnosis on EV genotype, especially for EV-71 and D-68 as 99.3% and 97.8%, respectively.

EV Genotyping is available at http://symbiosis.iis.sinica.edu.tw/Enterovirus/

Disclosure of Interest: None Declared

Synchronization effects on model parametrization for the yeast cell cycle

Julia Katharina Schlichting[*1], Gabriele Schreiber[1], Lisa Mallis[1], Edda Klipp[1]
[1]Theoretical Biophysics, HUMBOLDT-UNIVERSITÄT ZU BERLIN, Berlin, Germany

Your abstract : Saccharomyces cerevisiae is a famous model organism to study the mitotic cell cycle in eukaryotic cells. Cln2 and Clb5 (cyclins) as well as Sic1 (CKI) are key players in the regulation of the G1-S transition, called START. We measured the absolute number of mRNA molecules of unsynchronized single cells for SIC1, CLN2 and CLB5 by smFISH. Each cell was assigned to a specific cell cycle phase by using morphological markers, so that we get mRNA distributions per cell cycle phase. We quantified the relative number of protein molecules in a synchronized cell population for Sic1, Cln2 and Clb5 by Western blotting. The number of proteins is given as time course over the cell cycle.
In this study, we analyze differences between synchronization methods, as well as the difference between synchronized and unsynchronized cell populations. Chemical synchronizations are stronger than physical ones. We used α-factor as the most common chemical synchronization. Cells start with G1 after release. Further, we applied hydroxyurea and nocodazol, which release cells in S and G2, respectively. Elutriation is used for physical synchronization. Selected new born cells start with G1 after release. The goal is to gain insight, to what extent we can use synchronized cell populations to draw conclusions for unsynchronized cells.
We combine both data types to parameterize a stochastic model focusing on the key regulators for the G1-S transcripts by using a maximum likelihood approach. Our 2-step-optimization method differentiates between mRNA and protein levels. In our algorithms, we used a Poisson error model for mRNAs and a Gaussian error model for proteins. We used deterministic optimizers and multistart conditions to identify potential global optima. By means of calculating profile likelihoods we analyzed parameter identifiabilities. Including regularization, we figured out where our data don't cover the model.

Disclosure of Interest: None Declared

Temporal clustering analysis of endothelial cell gene expression under a conventional radiotherapy dose fraction using Gaussian process clustering

Markus Heinonen[1], Fabien Milliat[2], Mohamed Amine Benadjaoud[2], Agnès François[2], Valérie Buard[2], Georges Tarlet[2], Florence d'Alché-Buc[3], Olivier Guipaud[* 2]
[1]Department of Information and Computer Science, Aalto University, Espoo, Finland, [2]Human Health Unit, IRSN, Fontenay aux Roses, [3]LTCI, TELECOM ParisTech, Paris, France

Your abstract : The vascular endothelium is considered as a key cell compartment for the response to ionizing radiation of normal tissues and tumors, and as a promising target to improve the differential effect of radiotherapy in the future. Following radiation exposure, the global endothelial cell response covers a wide range of molecular changes with a global gene, miRNA, protein, metabolite expression pattern of modifications. Changes occur at the transcriptional, translational and post-translational levels and impact cell phenotype as well as also the microenvironment by production and secretion of soluble factors such as reactive oxygen species, chemokines, cytokines and growth factors. These radiation-induced dynamic modifications of molecular networks may control the endothelial cell phenotype and govern recruitment of immune cells, stressing the importance of clearly understanding the mechanisms which underlie these temporal processes. A wide variety of time series data is commonly used in bioinformatics studies, including gene expression, protein concentrations and metabolomics data. Utilizing clustering over them is still an unclear problem. Here, we introduce kernel between Gaussian processes modeling time-series, and subsequently introduce a spectral clustering algorithm. We apply the methods to the study of human primary endothelial cells (HUVECs) exposed to a radiotherapy dose fraction (2 Gy). Time windows of differential expressions of 301 genes involved in key cellular processes such as angiogenesis, inflammation, apoptosis, immune response and protein kinase were determined from 12 hours to 3 weeks post-irradiation. Then, 43 temporal clusters corresponding to profiles of similar expressions, including 49 genes out of 301 initially measured, were generated according to the proposed method. Forty-seven transcription factors (TFs) responsible for the expression of clusters of genes were predicted from sequence regulatory elements using the MotifMap system. Their temporal profiles of occurrences where established and clustered. Dynamic network interactions and molecular pathways of TFs and differential genes were finally explored, revealing key node genes and putative important cellular processes involved in tissue infiltration by immune cells following exposure to a fraction dose of radiotherapy.

Disclosure of Interest: None Declared

CoRC - the Copasi R Connector

Jonas Förster[1], Jürgen Pahle[* 2]
[1]DKFZ, [2]HEIDELBERG UNIVERSITY, Heidelberg, Germany

Your abstract : Copasi (http://www.copasi.org) is a biochemical simulator and model analyser which has found widespread use in academic research, teaching, and beyond. One of Copasi's strengths is its graphical user interface, and this is what most users work with. Copasi also provides a command-line tool. So far, an intuitive scripting interface that allows the creation and documentation of systems biology workflows was missing though.
We have developed CoRC, the Copasi R Connector, an R package which provides a high-level scripting interface for Copasi. It closely mirrors the thought process of a (graphical interface) user and is therefore very easy to use. At the same time, it allows for complex workflows to be reproducibly scripted, utilising Copasi's powerful analytic toolset in combination with R's (statistical) analysis and package ecosystem, and its extensive plotting functionality. CoRC can also be used to specify more computationally demanding workflows that are then sent to computer clusters and/or calculated in a parallel fashion.
We demonstrate the use of CoRC with a number of typical systems biology workflows implemented with CoRC and R Markdown notebooks.
CoRC is a free and open-source R package, available via GitHub at https://jpahle.github.io/CoRC/ under the Artistic-2.0 license.

Disclosure of Interest: None Declared

Efficient parameterization of large-scale dynamic models using relative protein, phospho-protein and proliferation measurements

Leonard Schmiester[1, 2], Yannik Schälte[1, 2], Fabian Fröhlich[1, 2], Jan Hasenauer[1, 2], Daniel Weindl[*1]

[1]Institute of Computational Biology, Helmholtz Zentrum München Deutsches Forschungszentrum für Gesundheit und Umwelt (GmbH), Neuherberg, [2]Center for Mathematics, Technische Universität München, Garching, Germany

Your abstract : Mechanistic models of signaling pathways provide the means to integrate heterogeneous data and to gain a quantitative understanding of cellular physiology. However, many models only focus on individual pathways, neglecting many others and ignoring any cross talk. Larger models on the other hand come with big challenges for parameter estimation, not only in the form of high computational demand. In particular, we found that relative measurements - which is what most large-scale datasets are - drastically impair optimizer performance.

In this study, we consider a large-scale ordinary differential equation model of cancer-related signaling (>4000 kinetic parameters, >1000 state variables) and parameterize it using relative measurements of protein, phospho-protein and proliferation data from cancer cell lines. We demonstrate the loss of information due to relative data and the associated decline in optimization robustness with different types of optimizers. We subsequently demonstrate how a novel hierarchical optimization approach in combination with adjoint sensitivity analysis can be applied to recover optimizer performance and parameterize large models. We show how our approach allows computing proportionality factors, offset parameters and error model parameters analytically, thereby simplifying the numerical optimization problem considerably and rendering it solvable by previously failing optimizers. Furthermore, we show that this approach allows us to estimate error model parameters with negligible computational overhead when no experimental estimates are available. The estimated distribution of measurement errors provides unbiased means to weight heterogeneous datasets. Finally, we show that integrating molecular data with phenotypical data improves model generalization when predicting drug response phenotypes of cancer cell lines.

Overall, our hierarchical optimization approach allows for the efficient parameterization of large-scale dynamic models based on heterogeneous relative measurements and can easily be adopted by other researchers.

Disclosure of Interest: None Declared

An algorithm for practical identifiability analysis and confidence intervals evaluation based on constrained optimization

Ivan Borisov[*1], Evgeny Metelkin[1]
[1]INSYSBIO LLC, Moscow, Russia

Your abstract : Objective: The reliability and predictability of a kinetic systems biology (SB) model depends on the calibration of model parameters. Experimental data can be insufficient to determine all the parameters unambiguously. This results in “non-identifiable” parameters and parameters identifiable within confidence intervals. The proposed algorithm is a practical implementation of Profile Likelihood [1] method for parameters identification which can be applied to complex SB models. The results of this algorithm can be used to qualify and calibrate parameters or to reduce the model.

Results: The proposed algorithm for Profile Likelihood method addresses the disadvantages and restrictions of the root-finding algorithms with regard to the above problem and utilizes the Inequality-based Constrained Optimization [2, 3] for efficient determination of confidence intervals and detection of “non-identifiable” parameters. This algorithm does not assume that the likelihood function is differentiable or can be calculated for any given parameters set. This algorithm can be applied to complex kinetic models where function differentiability is not guaranteed and each likelihood estimation is computationally expensive. The algorithm was tested for the set of kinetic models and it is distributed as a software package based on Julia Programming Language [4]. The package includes tools for parameters identifiability analysis, confidence intervals evaluation and results visualization.

Conclusion: The proposed algorithm and software package can be used as a means of identifiability analysis and confidence intervals evaluation for complex SB models.

References:

1. Kreutz C., et al. Profile Likelihood in Systems Biology. FEBS Journal 280(11), 2564-2571, 2013
2. Steven G. Johnson, The NLopt nonlinear-optimization package, http://ab-initio.mit.edu/nlopt
3. Andrew R. Conn, Nicholas I. M. Gould, and Philippe L. Toint, "A globally convergent augmented Lagrangian algorithm for optimization with general constraints and simple bounds," SIAM J. Numer. Anal. vol. 28, no. 2, p. 545-572 (1991)
4. Julia: A Fresh Approach to Numerical Computing. Jeff Bezanson, Alan Edelman, Stefan Karpinski and Viral B. Shah (2017) SIAM Review, 59: 65–98

Disclosure of Interest: None Declared

Real-time metabolism assessment using NMR analyzes: application to the optimization of energy usage in mammalian cell-free protein synthesis systems

Johan Perrier[*1], Baptiste Panthu[1], Benedicte Helena[2], Gilles Rautureau[2]
[1]CARMEN, [2]CRMN, LYON, France

Your abstract : Nuclear Magnetic Resonance (NMR) is well validated in the context of metabolomics studies as a powerful metabolic phenotyping platform that can contribute to biological investigations. Real-time NMR is a technical approach developed to study composition-evolving solutions by providing series of spectra that are followed over time, from which the sample composition and evolution can be characterized. As NMR can detect, identify and quantify numerous metabolites in a non-destructive manner and under physiological conditions (pH, temperature), it is uniquely suited to assess complex biological metabolic reactions: applied to fresh cell lysates (200 uL, obtained from culture cells, biological specimens or biopsies), real-time NMR allows to quantify substrates consumption (and metabolic pathways downside products evolution), after the addition of specific substrates to re-activate metabolic activities.

We illustrate how real-time NMR investigation of metabolites kinetics can deliver a detailed picture of the energetic metabolism for hybrid cell-free protein synthesis (CFPS) systems composed of rabbit reticulocyte lysates (RRL) ribosome-free supernatant complemented with ribosomes from different mammalian cell-types. A counterintuitive strategy, based on reducing the ribosomal fraction in RRL, is rationalized using a real-time NMR metabolomics investigation. We show that persistent ribosome-associated metabolic activity consuming ATP is a major obstacle for maximal protein yield, and reveal the potential of real-time NMR for optimization of CFPS systems.(1)

References

(1) Panthu B., Ohlmann T., Perrier J., Schlattner U., Jalinot P., Elena-Herrmann B., and Rautureau G. J. P., *ACS Synth. Biol.* Article ASAP, doi: 10.1021/acssynbio.7b00280 (2017).

Disclosure of Interest: None Declared

New E. coli bar-code deletion mutant library and its application of the monitoring of population dynamics by deep sequencing

Hirotada Mori[* 1, 2], Md Iqbal Nurhezreen[2], Ai Muto[1]
[1]Data Science Center, [2]Graduate School of Biological Sciences, Nara Institute of Science and Technology, Ikoma, Japan

Secondary topic : Methodological developments for Systems Biology

Your abstract : New E. coli K-12 bar-code single gene knockout mutant library has been constructed. Each target gene has two independent isolates as Keio collection. Each strain has 20 nt randomly synthesized sequence as bar-code. Once confirmed its deletion structure, bar-code sequence has been determined by sequencing.

To validate this new resource to monitor each of strains' population changes in the mixed culture, we first tried in long-term stationary phase condition. All of deletion strains independently cultured in LB using 96 well deep plate, then equal amount of culture of all of strains except mutator genes were mixed and glycerol was added to final concentration of 15%. 1ml aliquots were made and kept in -80ºC as seed stock. For monitoring, 1ml seed stock was added into 500ml LB and kept shaking at 37ºC for three weeks. 20ml culture was collected at each time point and chromosomal DNA was extracted from half of the culture as a time-series samples. The rest of culture was refreshed medium by 100 times dilution with fresh LB and cultured at 37ºC until reached to 1.0 OD600, then extracted chromosomal DNA as serial passage samples. From the chromosomal DNA, bar-code fragments were prepared by small cycle of PCR by primers set with sequencing adaptors and identifiers of each of samples. Once prepared, each sample were adjusted to equal DNA concentration and applied to deep sequencing. Raw DNA sequence reads were screened a few steps and finally bar-code frequency of each deletion strain was counted. Basic statistical validation and analysis were performed and applied enrichment analysis. Through these analysis, our new approaches could show good agreements with the previous knowledges shown as GASP phenotype with lots of additional anew suggestions.

The second challenge using this resource was drug tolerance problems. Mixed culture was incubated in LB medium containing sub-lethal (IC50) concentration of antibiotics (four bactericidal and three bacteriostatic antibiotics) for 24 hrs., and cells were transferred into higher concentration of drugs (IC70, IC90, 2xIC90) for 24 hrs. Sampling at every three hours were done and applied for bar-code sequencing and data-processing as described in the long-term stationary phase.

I would describe the new resource and show the first trials using this resource to analyses of LTSP, and drug tolerance and persister problems.

Disclosure of Interest: None Declared

KAMI: a bio-curation tool for cellular signalling

Eugenia Oshurko[*1], Russ Harmer[1], Sebastien Legare[1]
[1]ECOLE NORMALE SUPERIEURE DE LYON, Lyon, France

Secondary topic : Modelling Networks and Circuits

Your abstract : Rule-based modelling has proven to be a successful approach for studying complex systems of cellular signalling. A rule-based language Kappa has been actively developed and used in recent years. While being able to deal with the problem of combinatorial explosion in the number of molecular species particular to classical modelling techniques, Kappa stays unsuited for building and curating big explanatory models---for what we refer to as bio-curation. To tackle exactly this problem we propose a tool called KAMI (Knowledge Aggregator and Model Instantiator), which allows gradual semi-automatic aggregation of PPIs of different provenance, their annotation, visualisation and further instantiation to concrete rule-based models (including automatic generation of Kappa rules).

Models in KAMI are accommodated using a specially designed knowledge representation (KR) system based on hierarchies of graphs. This system provides a powerful and mathematically robust framework for meta-modelling: for representation of models on different abstraction levels, their syntax and semantics, as well as their audit and update. In this talk we will present the KR system and, in particular, its instance used for rule-based modelling of cellular signalling adopted in KAMI. Then we will speak about the strategy of automatic knowledge aggregation and instantiation that exploits the properties of this system. We will also show how domain-specific background knowledge such as semantics of conserved protein domains, definitions of protein families, splice variants and mutants is used in KAMI to sharpen aggregated models. And finally, we will present a model of tyrosine phosphorylation involved in cell signalling build with KAMI as an example of its use.

Disclosure of Interest: None Declared

Drug target detection in metabolic networks as an optimality problem

Olufemi Bolaji[*1], Edda Klipp[1]
[1]Theoretical Biophysics, Humboldt Universität zu Berlin, Berlin, Germany

Secondary topic : Modelling Networks and Circuits

Your abstract :

Optimality Principles have played a major role in biological systems, from describing mechanisms to being able to predict from first principles to the design of organisms.

In this work, we present a dynamic optimization strategy to determine drug targets of pathological dynamic metabolic networks. This methodology involves testing the influence of inhibitors, i.e. the control profiles, via different modes-of-action to the enzymes in the network, and driving the network to a desired healthy state through the maximization or minimization of one or multi-objectives set a priori.

The proposed solution of the optimization problem involves using a combination of ε - constraint and control vector parametrization (CVP) to obtain non-linear programming problem (NLP) and initial value problem (IVP), which are solved by enhanced scatter search (eSS) optimization metaheuristic implemented in the AMIGO2 toolbox [1].

Using a glycolysis dynamic-model of Trypanosoma brucei, we show a scan for vulnerable enzymes in the model that are probably good drug targets.

This project has received funding from the EU Horizon 2020 Research & Innovation Program under the Marie Skłodowska-Curie Grant Agreement #675585.

References

1. Balsa-Canto E., et al., (2016), Bioinformatics, 32, 3357.

Disclosure of Interest: None Declared

Modelling Networks and Circuits - MOD

SBML viewer is a tool for transformation of systems biology models to human-readable format

Viktoria Tkachenko[1], Evgeny Metelkin[*1]
[1]INSYSBIO LLC, Moscow, Russia

Secondary topic : Modelling Networks and Circuits

Your abstract : Objective: SBML is a free and open interchange format for computer models of biological processes maintained by the community. It is used in many modeling applications and can store model structure, math and annotation of elements. SBML is XML based format and designed basically for machine reading and writing. We are developing the approach and tool for fast and easy visualization of model components and navigation based on SBML file.
Results: We developed a series of transformations from SBML format to HTML which represents the content of SBML file in human-readable form. To perform file manipulations and transformations we developed the SbmlViewer web application which uses web-browser without any installation of third-party software. The last version of SbmlViewer allows visualization of SBML L2 and L3 using pure JavaScript and CSS styles. The uploading file to server is not required. The code was tested on series of models from SBML test engine and biomodels database. The application and XSLT transformations are freely available for use http://sv.insysbio.com and for downloading under Apache 2.0 license.
Conclusion: We are presenting a new version of SbmlViewer freely available online which can be used by systems biology modelers for model debugging, presentation and educational purposes.

Disclosure of Interest: None Declared

Quantifying information transfer in in silico gene regulatory networks

Diane Adjavon[* 1], G. Soorya[2], Arnaud Bonnafoux[1], Ulysse Herbach[1], Nicolas Garnier[3], Olivier Gandrillon[1]

[1]LBMC, ENS Lyon, Lyon, France, [2]Department of chemical engineering , Indian institute of technology, Madras, Chennai, India, [3]Laboratoire de Physique, ENS Lyon, Lyon, France

Secondary topic : Methodological developments for Systems Biology

Your abstract : The interactions between genes and their products within a cell can be modeled as a network. While this gene regulatory network (GRN) plays a central role in the development and differentiation of cells, the specifics of these interactions remain unknown for the most part. Study of the GRN exclusively through biological experiments can be long and expensive. The modeling and simulation of GRNs is therefore an active area of research in systems biology. We recently introduced a mechanistic model of gene expression at single-cell level, and suggested a function to model interactions between genes[1]. In order to evaluate different GRN architectures within the framework of this model, we required tools able to detect the complex, non-linear interactions between our in silico genes.

In this study, we show that transfer entropy is able to reliably measure directed information transfer during gene activation in simulation. As it leverages the power of single-cell data, it is also able to retrieve this information in situations where dynamics are either not visible or not separable at a population level. A promising tool for the study of complex dynamics in the framework of our model, we further believe that the application of transfer entropy could be extended to in vitro data if used in concert with results obtained by an inference framework based on the same underlying model as our simulations.

[1] Ulysse Herbach, Arnaud Bonnaffoux, Thibault Espinasse, and Olivier Gandrillon. Inferring gene regulatory networks from single-cell data: a mechanistic approach. BMC Systems Biology, 11(1), December 2017. arXiv: 1705.03407.

Disclosure of Interest: None Declared

SABIO-RK - kinetic data for systems biology

Andreas Weidemann[1, 1], Martin Golebiewski[* 1], Ulrike Wittig[1], Maja Rey[1], Wolfgang Müller[1]
[1]HITS GGMBH, HEIDELBERG, Germany

Secondary topic : Methodological developments for Systems Biology

Your abstract : SABIO-RK (http://sabiork.h-its.org/) is a manually curated database containing biochemical reactions and their kinetics together with their specifications (experimental conditions, organism, EC number etc.). It is a valuable resource for modellers simulating biochemical networks as well as for experimentalists interested in enzymatic activities and reaction properties. Kinetic data of metabolic, transport and signalling reactions included in SABIO-RK are mainly derived from literature, but also from SBML encoded models or directly from lab experiments. More than 22.500 database entries (38 % of all entries) refer to mammalian, therof 10.800 to human only. Several ontologies are embedded as Gene Ontology (GO) for cell locations and signalling events, Systems Biology Ontology (SBO) for kinetic laws and parameters and the Brenda Tissue Ontology (BTO). The predominant tissue arising in SABIO-RK is the liver with >8.800 entries (15.4 %) thereby giving information not only about wildtype but also mutated proteins. The data in SABIO-RK contain annotations to controlled vocabularies and are highly interlinked with other databases (KEGG, UniProt, BRENDA, Pubmed, ExPAS, Cellosaurs and others).
SABIO-RK can be accessed via an easy-to-use web interface or programmatically via RESTful webservices or Python scripts. Search results can be exported in different formats including SBML, XML and as spreadsheets. Actually SABIO-RK is accessed mainly (about 90 %) via web services, which underlines the importance of its integration into modelling and visualization tools like CellDesigner, VirtualCell, Sycamore, SBMLsqueezer, cy3sabiork, Path2Models, LigDig and FAIRDOMHub.
As part of de.NBI (German Network for Bioinformatics Infrastructure) we offer user support as trainings, knowledge exchange via google groups and the manual extraction of kinetics data from the literature upon user requests.

Disclosure of Interest: None Declared

Robustness of nutrient signalling is maintained by interconnectivity between signal transduction pathways

Niek Welkenhuysen[*1], Barbara Schnitzer[1], Linnea Österberg[1,2], Marija Cvijovic[1]
[1]Department of Mathematical Sciences, Chalmers University of Technology and the University of Gothenburg, Gothenburg, [2]Department of Biology and Biological Engineering, Chalmers University of Technology, Gothenborg, Sweden

Secondary topic : Modelling Networks and Circuits

Your abstract : Crosstalk in biology is any phenomenon by which an intracellular signal transmitted in one signalling pathway creates an effect in another pathway. In nutrient signalling pathways crosstalk has an important function. Typically, to study these pathway interconnections perturbation of the signalling system is involved. Unfortunately, perturbations often produce noise which causes a major challenge in identification of interconnections. Employing systems biology approach by developing appropriate models can provide minimal intervention in these systems. Signalling pathways are usually modelled by ordinary differential equations, however, creating dynamical models of signalling pathways of a realistic size is still an obstacle. To overcome this problem, we developed a vector-based reaction-contingency Boolean logic model of the yeast *Saccharomyces cerevisiae* nutrient sensing pathways cAMP-PKA, Snf1, Snf3-Rgt2 and TOR pathway. To increase the information content of Boolean model from simple 'active' and 'inactive', we assigned a vector to each component describing following features: localization, phosphorylation status, guanylation status and DNA binding status. This model approach is highly modular and easy to expand to other signalling pathways. We further found during the gap filling process that most lacking components are phosphatases which exposes a lack of knowledge on phosphatases involved in the sensing process. The gap filling process also identified crosstalk from the PKA and Snf1 pathway to other pathways as a vital aspect to make the model switch between nutrient conditions. We simulated the model with known crosstalk combinations. Subsequent analysis of the simulations that the crosstalk from the Snf1 pathway to the Rgt2/Snf3 pathway contributes to the robustness of this signalling network. Altogether, this work shows that network interconnections lead to the robustness of signalling pathways. Our approach contributes to the understanding of the function and importance of crosstalk in nutrient signalling.

Disclosure of Interest: None Declared

Pheromone gradients bias the directionality of the movement of a polarity site in yeast

Debraj Ghose[* 1], Katherine Jacobs[1], Samuel Ramirez[2], Timothy Elston[2], Daniel Lew[1]
[1]Pharmacology and Cancer Biology, DUKE UNIVERSITY, Durham, [2]Pharmacology, University of North Carolina, Chapel Hill, Chapel Hill, United States

Secondary topic : Developmental Systems Biology

Your abstract :

Eukaryotic cells such as cancer cells, fibroblasts, developing neurons, and budding yeast grow (chemotropism) or move (chemotaxis) in a specific direction in response to spatial chemical gradients. We study the chemotropic mating response in the genetically tractable budding yeast *Saccharomyces cerevisiae* as a model for eukaryotic gradient tracking. Haploid budding yeast have been shown to grow up gradients of yeast pheromones to fuse with their mating partners. The growth is oriented towards the polarity site, a cortical region enriched in the Rho-GTPase Cdc42 and its regulators and effectors. G-protein coupled receptors that sense pheromone are secreted at the polarity site and enriched in the local plasma membrane, generating a local pheromone-sensitive zone or “nose”. A cell in a pheromone gradient may form a polarity site anywhere on its cortex, but the site can then migrate in an erratic manner; and when polarity sites in mating partners align towards one another, the cells can mate. Migration of the polarity site means that the “nose” can sample the pheromone landscape around the cell. Studies conducted with cells exposed to uniform pheromone show that movement slows with increasing levels of pheromone. We report that a computational model of the polarity site constructed to reflect its behavior in uniform pheromone can successfully track steep pheromone gradients. Simulations were employed to dissect whether this tracking was dependent on pheromone-mediated changes in the degree of movement or the direction of movement, demonstrating that the vast majority of the tracking arose from pheromone-biased directionality of the movement. This was experimentally confirmed for yeast cells *in vivo*. Our model indicates that the directional bias arises as a consequence of differentially occupied receptors across the width of the remarkably small (1 micron radius) nose. While noise due to stochastic binding and unbinding of pheromone molecules with receptors might be expected to overwhelm the small signal, our simulations suggest that yeast cells can focus a sufficient number of receptors at the nose to overcome the chemical noise in ligand-receptor interactions.

Disclosure of Interest: None Declared

Coordination of mRNA stability and cell physiology in bacteria: a modelling study

Thibault Etienne[* 1, 2, 3], Laurence Girbal[2], Muriel Cocaign-Bousquet[2], Delphine Ropers[1]
[1]Univ. Grenoble – Alpes, Inria, Grenoble, [2]LISBP, INSA/CNRS 5504 - UMR INSA/INRA 792, Toulouse, [3]Univ. Lyon 1, Lyon, France

Secondary topic : Multi-omics

Your abstract : Bacteria have evolved strategies for growing in a variety of environmental conditions. These notably involve a reprogramming of gene expression at the post-transcriptional level to adjust protein concentrations to the cell needs. Contrary to the often-made assumption in bacteria, protein and mRNA levels are not always proportional and mRNA stability (typically a few minutes) varies with the translational activity, the cell growth rate and the concentration of regulators (small RNAs, HFQ...). How these various interlocked control mechanisms adjust mRNA half-life to cell physiology remains largely unknown.

We tackle this question by using a comprehensive –omics data set on mRNA decay in the bacterium *Escherichia coli*. These time-series data have been used recently to determine mRNA half-lives in various steady-state growth conditions (Esquerré *et al.*PMID 24243845,PMID 25887031). We aim at proposing a mechanistic explanation for the adjustment of mRNA stability to the growth rate of *E. coli*. For this, we develop a structural model of mRNA degradation by the limiting ribonuclease of *E. coli*, RNase E. We hypothesize that the mechanism of mRNA degradation by RNase E is common to all messenger RNAs, but that the kinetics of the degradation varies between mRNAs and growth conditions because of (global and specific) regulatory mechanisms: changes between growth rates of the concentrations of RNAse E, of small RNAs...

For each of the 4254 genes and of the four growth rates, the mRNA decay is described by means of a Michaelis-Menten scheme. The model parameters vary with the nature of the mRNA and the cell growth rate. A mixed-effect modelling framework is used to take into account their variability: using the time-series –omics data, we estimate the mean parameters describing the population of mRNAs and the variance parameters, which allow to reproduce the degradation profile of each mRNA in each condition.

The analysis of mean parameter values shows that global regulatory effects adjusting the concentration of RNase E and mRNAs shape the degradation profile of the majority of mRNAs at different growth rates. The clustering of random effects shows that additional specific regulatory mechanisms fine-tune the stability of subsets of mRNAs. The clusters are enriched in genes for which a regulatory mechanism is known in the literature. This allows us to propose regulatory mechanisms for the remaining genes of the clusters, which will be further validated experimentally.

Disclosure of Interest: None Declared

Narrowing down uncertainty in yeast central carbon metabolism: an extended kinetic model to understand effects of dynamic environments.

David Lao-Martil[* 1], Joep P. J. Schmitz[2], Bas Teusink[3], Natal A. W. van Riel[1] on behalf of Computational Biology

[1]Biomedical engineering, TU/E, EINDHOVEN UNIVERSITY OF TECHNOLOGY, Eindhoven, [2]DSM Food Specialities, Delft, [3]Sytems bioinformatics group, VU, Vrije Universiteit Amsterdam, Amsterdam, Netherlands

Secondary topic : Multiscale Systems Biology

Your abstract : How extensive can a kinetic metabolic network be? How many parameters can be taken into account, without deteriorating simulation efficacy? Could this metabolic network be used to predict behavior under different environments? Parametric and topological uncertainties in kinetic models burden our answer to these questions[1]. Predicting how parameter values change from *in vitro* to *in vivo* conditions is still not possible[2]. In addition, how network regulation occurs at transcriptional and posttranslational levels is not fully understood[3].

In the current project, we are developing a comprehensive kinetic model of yeast central carbon metabolism that accounts for glycolysis, pentose phosphate pathway, trehalose and glycogen metabolism, Krebs cycle and oxidative phosphorylation. Furthermore, the model aims to predict behavior under dynamic environmental conditions, such as changing carbon sources and oxygen concentrations that are found in industrial conditions. For model development, a previously existing network[2] was used as a starting point, and developed with published literature and our own experimental data. For modeling purposes, the Analysis of Dynamic Adaptations in Parameter Trajectories (ADAPT)[4] algorithm has been used. This method carries out parameter estimation in a previously defined deterministic model, but it allows parameter values to change with time in order to fit the experimental dataset. By doing so, places in the network with topologic uncertainty may be identified.

A network with glycolysis, trehalose and glycerol metabolism and oxidative phosphorylation has been generated. Data has been obtained from growth in bioreactors where extracellular glucose concentrations were varied. The simulations have pointed out at some enzymes in the network, such as phosphofructokinase (PFK) cannot be accurately modelled with the current knowledge, and thus require a more refined definition of its kinetics.

Currently, the algorithm has pointed out regions where topological uncertainty in the model needs improvement. Still the model coverage is far from the ultimate goal, and increasing this is the aim for future research. This ongoing research is found within the Yeast 3M project[5].

Keywords: Yeast central carbon metabolism, kinetic metabolic network, multilevel regulation, parameter estimation, dynamic environments, parametric and topologic uncertainties, PFK, Yeast 3M project, ADAPT.

Disclosure of Interest: None Declared

Logical modelling and network analysis of cellular metabolic flexibility

Samar Tareen[*1], Martina Kutmon[1], Theo de Kok[1], Ilja Arts[1], Chris Evelo[1], Michiel Adriaens[1] and Maastricht Centre for Systems Biology (MaCSBio)
[1]Maastricht Centre for Systems Biology (MaCSBio), MAASTRICHT UNIVERSITY, Maastricht, Netherlands

Secondary topic : Multiscale Systems Biology

Your abstract : Metabolic flexibility is the ability of an organism to switch its substrate for cellular metabolism depending on nutrient availability. In humans, and in most other higher organisms, this materialises as the ability of most cells to switch from glucose to fatty acids, and vice versa. Metabolic flexibility in humans is maintained at both the cellular and the organism level considering different cell types have different metabolic requirements at different times. The signalling needed between these two levels to maintain metabolic flexibility is tightly regulated, especially at the cellular level where the metabolites themselves play a regulatory role by interacting with cellular proteins.
We model the cellular metabolic flexibility revolving around the TCA cycle, thus the oxidative metabolism of glucose and fatty acids for energy production. We utilised the René Thomas kinetic modelling framework for discrete/logical modelling of the regulatory network, using the software GINSim. System verification on known biological behaviours was performed using computation tree logic (CTL) model checking via the SMBioNet tool. We focus primarily on the regulatory interactions of pyruvate dehydrogenase kinases (PDKs) on the pyruvate dehydrogenase complex (PDC), namely the inhibition of PDC by PDKs via site specific phosphorylation.
We modelled four possible regulatory scenarios of the PDK isoenzymes, each generating its own graph of all possible behaviours, called state graphs. We then performed network analysis on said state graphs to find subnetworks to compare the four scenarios with each other, thus assessing the impact of each regulatory mechanism of PDKs. We observed that regardless of the regulatory mechanism, the biological system in all four scenarios eventually settled into the same or very similar dynamics, indicating the biological plausibility of all four scenarios. We further assessed the system by performing a perturbation analysis on the negative regulators in the biological regulatory network in the four scenarios. We observed that regardless of which negative regulatory protein(s) is perturbed, the effect always propagated via the PDKs regulation of PDC, indicating that the PDC-PDK regulatory interaction is the driving force behind cellular metabolic flexibility, the perturbation of which leads to metabolic inflexibility, and thus other metabolic issues down the line such as lipotoxicity and impaired insulin signalling.

Disclosure of Interest: None Declared

Enzyme economy in metabolic networks

Wolfram Liebermeister[*1]
[1]MIA - Research Unit MaIAGE, INRA, Jouy-en-Josas, France

Secondary topic : Quantitative Systems Physiology

Your abstract : Metabolic systems are governed by a compromise between metabolic benefit and enzyme cost. This hypothesis and its consequences can be studied by kinetic models in which enzyme profiles are chosen by optimality principles. In enzyme-optimal states, active enzymes must provide benefits: a higher enzyme level must provide a metabolic benefit to justify the additional enzyme cost. This entails general relations between metabolic fluxes, reaction elasticities, and enzyme costs, the laws of metabolic economics. The laws can be formulated using economic potentials and loads, state variables that quantify how metabolites, reactions, and enzymes affect the metabolic performance in a steady state. Economic balance equations link them to fluxes, reaction elasticities, and enzyme levels locally in the network. Economically feasible fluxes must be free of futile cycles and must lead from lower to higher economic potentials, just like thermodynamics makes them lead from higher to lower chemical potentials. Metabolic economics provides algebraic conditions for economical fluxes, which are independent of the underlying kinetic models. It justifies and extends the principle of minimal fluxes and shows how to construct kinetic models in enzyme-optimal states, where all enzymes have a positive influence on the metabolic performance.

Disclosure of Interest: None Declared

Application of parallel runs of global stochastic optimization methods in COPASI wrapper SpaceScanner for termination of optimization task

Agris Pentjuss[*1], Egils Stalidzans[1]
[1]Institute of Microbiology and Biotechnology, UNIVERSITY OF LATVIA, Riga, Latvia

Secondary topic : Systems Biology for Synthetic Biology

Your abstract : One of demanding tasks in systems biology is the optimization of non-linear kinetic models described in the form of ordinary differential equation systems. *COPASI* wrapper *SpaceScanner* is developed to automate this process, specially dealing with combinatorial explosion of adjustable parameters.

In case of automation of optimization it is important to use universal optimization methods and have option to change methods automatically if some of them do not perform well. Due to their universal applicability, *SpaceScanner* uses global stochastic optimization methods implemented in *COPASI* software. The drawbacks of global stochastic optimization methods are: (i) no guarantee of finding global optima, (ii) no clear optimization run termination criteria and (iii) no criteria to detect stagnation of an optimization run. *SpaceScanner* addresses these drawbacks: performance of parallel optimization runs with identical optimization task setting is analyzed to detect consensus or stagnation cases. Consensus is found when all parallel runs have values within pre-defined tolerance range for pre-defined time period. That means, optimal value is reached with some confidence that depending on the settings of *SpaceScanner*. Stagnation is registered when none of parallel runs have changes in values for a pre-set time period and value of at least one run is different from others more than the pre-defined tolerance. Stagnation indicates that particular method should be changed.

SpaceScanner automatically performs: (i) parallel optimization runs with automated recognition of consensus and stagnation situations, (ii) automatic switching between different user-selected global stochastic optimization methods in case of stagnation in the current method, (iii) determination of the best sets of adjustable parameters for a pre-set range of a number of adjustable parameters in combination and (iv) search for the minimal number of adjustable parameters that can reach the requested fraction of the total optimization potential (TOP).

SpaceScanner can have more conservative settings: (i) increasing number of parallel runs, (ii) reducing consensus corridor and (iii) increasing delay time settings. Thus, if high confidence about reaching global optima is needed (still with no guarantee), conservative consensus criteria may be used requiring increased time and computational costs of optimization. When looking for a fast preliminary scan of solution space, settings may be more relaxed.

Disclosure of Interest: None Declared

Bayesian modelling to predict the evolution of eczema severity

Guillem Hurault[*1], Reiko Tanaka[1]
[1]Department of Bioengineering, IMPERIAL COLLEGE LONDON, LONDON, United Kingdom

Secondary topic : Systems Medicine

Your abstract : Atopic dermatitis (AD), or eczema, is a most common chronic skin disease characterised by a dry and itchy skin. The disease pathogenesis is governed by a dynamic interplay between skin barrier, immune responses, and environmental stressors. Given a large variation in the disease severity and responses to treatments from one individual to another, it is of high clinical relevance to design personalized treatment strategies for AD, rather than the "one-fits-all" treatments. Better prognoses of the course of AD severity could help to choose appropriate treatments for each patient. In this study, we aim to develop a statistical model that can predict the short-term course of the eczema severity by fitting clinical data to a previously developed mechanistic model of AD pathogenesis ("double-switch model").

We used the data from an already published longitudinal clinical study on 60 AD children under a topical corticosteroid therapy. The data included daily self-assessment of two eczema severity scores and environmental exposures, for up to 9 months. We developed a Bayesian graphical model of the evolution of eczema severity based on the double-switch model, performed inference using Markov Chain Monte-Carlo (MCMC) and validated the predictions in an online learning setting.

The proposed probabilistic model to predict the short-term course of eczema severity improved chance-level predictions by 50% as measured by the Ranked Probability Skill Score, confirming that the model could learn AD dynamics as more data becomes available. We also estimated patient-dependent parameters such as the rates of occurrence and persistence of inflammation. These parameters could be used to stratify patients based on whether the disease is controlled or not and whether the current treatment is effective or not.

In conclusion, we developed and internally validated a statistical model to predict the short-term course of eczema severities. Similar models could be developed to assess the effects of different treatments on the dynamic course of eczema severities. The method used here will be tested with another patient population data, as the data used in this study was from a relatively small number of patients who might not be representative of the general population.

Disclosure of Interest: None Declared

Network modeling and systems analysis reveal epithelial-to-mesenchymal transition spectrum and novel synergistic targets for its reversion

Namhee Kim* [1], Yunseong Kim[1], Kwang-Hyun Cho[1]
[1]Department of Bio and Brain engineering, KAIST, Daejeon, Korea, South

Secondary topic : Systems Medicine

Your abstract : Network modeling and systems analysis reveal epithelial-to-mesenchymal transition spectrum and novel synergistic targets for its reversion

Namhee Kim, Yunseong Kim, Kwang-Hyun Cho*

Laboratory for Systems Biology and Bio-inspired Engineering, Department of Bio and Brain Engineering, Korea Advanced Institute of Science and Technology (KAIST), Daejeon, 34141, Republic of Korea

The Epithelial-to-Mesenchymal Transition (EMT) is a key process in tumor progression, metastasis, and drug resistance. During the transition from epithelial to mesenchymal phenotype, cells lose cell-cell adhesion and gain invasiveness either partially or completely that are often observed as a hybrid phenotype. The hybrid phenotype is an intermediate state having both epithelial and mesenchymal characteristics. These traits enable cells to migrate collectively and to gain more metastatic potential than mesenchymal cells. Previous studies proposed that a hybrid phenotype is associated with drug resistance. However, the mechanism of how the hybrid phenotype occurs with non-classical EMT-associated feature and how it acquires drug resistance are largely unknown. To solve this puzzle, we have constructed a Boolean network model of EMT by integrating key regulatory interactions from experimental data. Then, we investigated the mechanism of acquiring the hybrid properties by simulating and analyzing the overall dynamics of phenotypic plasticity during EMT. We found that overcoming the hybrid phenotype might be a key for reversing EMT completely without inducing drug resistance. The results of this study provide us with a new perspective on drug-resistant phenotype and also substantiate our understanding on previous observations of why the conventional drug is not enough to reverse EMT completely.

Acknowledgements:
This work was supported by the KAIST Future Systems Healthcare Project from the Ministry of Science and ICT, and the National Research Foundation of Korea (NRF) grants funded by the Korea Government, the Ministry of Science and ICT (2017R1A2A1A17069642 and 2015M3A9A7067220).

* Corresponding author, E-mail: ckh@kaist.ac.kr, Phone: +82-42-350-4325, Fax: +82-42-350-4310, Web address: http://sbie.kaist.ac.kr.

Disclosure of Interest: None Declared

Analysis of interconnections and dependencies between NF-κB signaling pathways using logical modeling

Kirsten Thobe[*1], Jana Wolf[1]
[1]Max Delbrück Center for Molecular Medicine, Berlin, Germany

Secondary topic : Systems Medicine

Your abstract : The nuclear factor kappa B (NF-κB) family of transcription factors are key players for coordinating inflammatory responses, proliferation, immune development and were shown to be often deregulated in cancer. These transcription factors themselves are tightly regulated by two different pathways: the canonical (or classical) NF-κB pathway and the non-canonical (or alternative) pathway. Despite the fact that these pathways were described to be two separate processes, there is an overlap in involved components from receptors to target genes, e.g. TRAF2, p100, IKKα.

Based on extensive literature research, we combine both pathways in one comprehensive logical model to explore interdependencies between the pathways. For this aim, separate models for each pathway were built and their behavior validated using literature data. Subsequently, the models were connected by shared components and observed crosstalk while preserving the behavior of the respective pathways.

Using the software PyBoolNet as well as GINsim, the resulting comprehensive NF-κB model is analyzed for control modules that determine the asymptotic behavior of the system and therefore are interesting for manipulations to stir the model towards a desired attractor. As a result, simulations for cancer-related deregulations further increase the understanding of the interplay of these modules in disease and aid to develop interventions strategies.

Disclosure of Interest: None Declared

Distribution of control in the sulfur assimilation in Arabidopsis thaliana depends on environmental conditions

Anna Feldman-Salit[1], Nadine Veith[*1], Markus Wirtz[2], Rüdiger Hell[2], Ursula Kummer[1]
[1]Modeling of Biological Processes, BioQuant/ Centre for Organismal Studies (COS), Heidelberg University, [2]Plant Molecular Biology , Centre for Organismal Studies (COS), Heidelberg University, Heidelberg, Germany

Secondary topic : Evolutionary and Ecological Systems Biology

Your abstract : Sulfur assimilation is central to the survival of plants and predominantly takes place in leaf mesophyll cells. The uptake of sulfur in form of sulfate by root cells has been studied under various environmental conditions. Reverse genetics approaches revealed rate-limiting steps of the sulfur assimilation pathway under optimal sulfur supply. However, the picture remains inconclusive with at least two enzymes, APR (adenosine-5'-phosphosulfate reductase) and SiR (sulfite reductase), proposed to play a central role in flux control.
Here, we used computational modeling to understand the distribution of control in the sulfur assimilation of *Arabidopsis thaliana* in response to the environment. We set up a new computational model of the sulfur assimilation pathway encompassing all biochemical reactions and cellular transport processes present in leaf cells. We fitted this model to published experimental data and produced a model ensemble to deal with parameter uncertainties. Next, this model ensemble was validated against an independent set of experimental data.
The validated model ensemble allowed us to analyze control pattern and robustly identify reactions that share control. Interestingly, but not expectantly, the control pattern was not static but dynamically responded to alterations in environmental conditions (e.g., external sulfate supply). While APR and SiR share control under optimal sulfur supply, APR plays a dominant role for the regulation of the flux through the pathway upon sulfur starvation.
Our approach revealed a molecular explanation for the experimentally confirmed dynamic regulation of APR in response to sulfur supply and the static abundance of SiR under all tested sulfur regimes.

Disclosure of Interest: None Declared

Analysis of potential drug targets for non-alcoholic fatty liver disease in a computational model

William Ashworth[* 1, 2], Nathan Davies[3], David Bogle[4]
[1]CoMPLEX (Centre for Computation, Mathematics and Physics in the Life Sciences and Experimental Biology), University College London, London, United Kingdom, [2]Cell Signal Unit, Okinawa Institute of Science and Technology, Okinawa, Japan, [3]Institute of Liver and Digestive Health, [4]Chemical Engineering, University College London, London, United Kingdom

Secondary topic : Systems Medicine

Your abstract : Hepatocytes, the main functional cells of the liver, receive blood through capillaries which extend from the hepatic artery and portal vein (periportal end) to the central vein (pericentral end). On a large scale, the liver appears functionally homogenous. However, on the micro-scale, depending upon their position along these capillaries, hepatocytes experience differences in the concentrations of nutrients, toxins, metabolic intermediates hormones and oxygens. To compensate, they show large variation in enzyme expression and function. These differences, known as zonation, are largely ignored in studies of liver disease due to the technical difficulty of studying experimentally. However, zonation is known to play a role in a wide range of liver diseases. Non-alcoholic fatty liver disease (NAFLD) is a condition in which fats build up in the liver (steatosis) due to lifestyle or genetic causes. In NAFLD, pericentral hepatocytes are known to be most susceptible to steatosis, fibrosis and inflammation. In a previous study, we used a computational model of hepatic metabolism along the capillaries to analyse the counterintuitive mechanisms leading to this pattern of steatosis (Ashworth et al., PLOS Comp. Bio. 12(9), 2016). Here, we use this model to assess the impact of targeting various metabolic pathways in NAFLD. Additionally, we validate key findings through a small number of cell culture experiments.

The effects of targeting several potential hepatic metabolic pathways were simulated in the model by altering the rate constants of the limiting enzymes. Almost all potential targets were associated with adverse effects such as disturbed ATP synthesis or increased precursors of oxidative stress. In most cases, these were most severe in hepatocytes residing in a particular region of the capillary, highlighting the importance of studying zonation. However, stimulation of β-oxidation in combination with inhibition of lipogenesis was predicted to effectively reduce steatosis in hepatocytes across the capillary whilst additionally improving ATP levels and reducing the precursors of mitochondrial stress. To test this experimentally, lipogenesis was inhibited whilst β-oxidation was allosterically stimulated using acetyl-CoA (1 and 2) inhibitor TOFA in HepG2 cells. Consistent with model predictions, treatment cleared steatosis, reduced oxidative stress, partially restored mitochondrial function and ATP concentrations, and reduced lipotoxicity-induced cell death.

Disclosure of Interest: None Declared

Kinetic models for frequency-decoding in calcium signalling - how topology and parameterization allow for band-pass activation

Arne Schoch[*1], Jürgen Pahle[1]
[1]Biological Information Processing Group at the BioQuant Center at Heidelberg University, Heidelberg, Germany

Your abstract : Several agonists were found to activate intracellular signaling cascades resulting in the emergence of oscillations in the cytosolic calcium levels in non-excitable cells. Dependent on the kind and abundance of the agonist, the shapes of these oscillations vary – frequency, amplitude, duration as well as the general shape (for instance, spiking or bursting oscillations) are all determined by the stimulation. As a second messenger, calcium interacts with a broad range of proteins controlling diverse cell functions. Hence, calcium needs to link the different stimuli with their corresponding cellular function in a reliable manner. Experimental studies reported, that selective activation is enabled by the proteins' sensitivity for particular oscillation characteristics. For instance, proteins display different levels of activity dependent on the frequency of oscillations.
For most proteins, activity increases with increasing frequencies. For the transcription factor NF-AT, however, a band-pass activation mechanism was observed. In detail, NF-AT's activity appears to be optimal for a particular frequency with frequencies lower or higher leading to a reduced activity.
We constructed and analyzed several models for the activation of proteins by calcium oscillations with different topologies, ranging from more abstract models to a specific model for the activation of NF-AT. We used optimization methods to find systems best suited for band- or high-pass activation identifying topological and parametric requirements. One important finding is the necessity of cooperative binding of calcium ions to a protein for pronounced frequency-decoding.

Disclosure of Interest: None Declared

Investigating strategies for cell fate conversion through the theoretical analysis of multistable gene regulatory networks

Rushina Shah[*1], Domitilla Del Vecchio[1]
[1]Department of Mechanical Engineering, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, Cambridge, United States

Your abstract : Inducing cell fate conversion using external inputs has tremendous applications in the study of cell development, disease modeling, and in the fields of therapeutic and regenerative medicine. In the past two decades, much progress has been made in triggering conversions between different cell types. However, current selection of stimuli to induce these conversions relies on biological intuition and trial-and-error, making the process lengthy and error-prone. In fact, it has been theoretically shown in certain cases that intuitive inputs may not be the most effective strategy, depending on the target cell phenotype and gene regulatory network (GRN) topology. To this end, in this poster, I will investigate strategies for cell fate conversion based on the theoretical analysis of certain core multistable GRN models. These core GRNs have been implicated in cell fate decisions, and many have been experimentally characterized, such that at least their topology is known. Applying theoretical tools from nonlinear dynamical systems to these mathematical models of the GRNs, I will show that in many cases, depending on the target state, currently used intuitive inputs may not be the most effective. I will further propose alternative strategies for these cases, considering experimentally convenient inputs such as induced overexpression or enhanced degradation of key transcription factors. Our mathematical results are validated through numerical simulations using Hill-function based ordinary differential equation (ODE) models. Experimental validation will be required to verify the efficacy of the proposed strategies. These mathematical results can provide a first step toward systematic ways to select inputs to induce specific cell fate conversions, and can potentially reduce the time and resources spent to select such inputs.

Disclosure of Interest: None Declared

A comprehensive logical model definition of insulin receptor

Ertuğrul Dalgiç[* 1]
[1]Medical Biology, Bulent Ecevit University School of Medicine, Zonguldak, Turkey

Your abstract : Modeling is inevitable for analyzing the dynamics of biological systems at molecular level. However, highly quantitative kinetic models simplify the real system in terms of the number of elements, because of a need of plenty of parameters and complexity. Logical modeling is a good alternative as it is better at handling complexity and it does not require many parameters. However, most logical studies do not use the full advantage of this modeling approach to define and analyze a biological system in a realistically complete way. In order to exploit the full potential of logical modeling, the number of inputs and outputs of a logic gate should be higher than what was used in previous studies. Here, an attempt to define a comprehensive logical definition of Insulin Receptor (IR) is discussed. Protein-protein interaction partners of IR were obtained from a literature-based interaction database. A manual curation of the IR neighborhood was done to define inputs and outputs of the IR logic gate. Activities of the proteins in the IR neighborhood was obtained from a public database. The protein expression levels were supposed to represent the activities of proteins. Expression/activity levels of proteins were also used to support the signed directions of the IR neighborhood. As a result, logic gates of IR were constructed for various cell types and compared to each other, which was omitted in classical logical modeling approaches. Construction of logical models using more comprehensive gates such as the one presented in this study, would yield better analyses of biological systems. Successful implementation of these models could also let us make comparison to other systems such as electronic circuits where logic gates have very limited number inputs.

Disclosure of Interest: None Declared

Exploring temperol differences between gene activity of neonatal, senescent and adult fibroblasts using high throughput qPCR and mechanistic modelling

Ciaran Welsh[*1], Nicola Fullard[2], Stefan Przyborski[2], Daryl Shanley[1]
[1]Health and medical science, Newcastle University, Newcastle, [2]Department of Biosciences, Durham University, Durham, United Kingdom

Secondary topic : Multi-omics

Your abstract : Skin is a complex and heterogeneous tissue where both epidermal and dermal skin compartments constantly undergo turnover, remodelling their structure in response to biochemical cues such as TGFb. With age, the composition of skin is compromised rendering aged tissue less able to perform its functions. There are some known differences between old and young dermis but a more complete understanding would help us in efforts to restore function. In this study we have performed a high throughput qPCR experiment to measure the dynamics of 72 transcripts that either encode ECM or TGFb signalling proteins. The experiment was performed with and without TGFb stimulation for 12 time points over 96h in 3 cell lines apiece for neonatal, irradiation-induced senescent and adult cell lines. Our results show that clear differences exist in the dynamics of the selected genes when comparing the different cell lines. Moreover, our statistical analysis provides an indication of which genes are different between groups. The data collected in this experiment is available for exploration in a web application designed for interactively exploring this dataset (http://cwelsh2.pythonanywhere.com). Finally, a small selection of the data has been used to inform a mechanistic model that proposes connective tissue growth factor (CTGF) dynamics as critical in TGFb-induced collagen production. Collectively this work furthers our understanding of how age and senescence affects the dermis which is an essential step that precludes the understanding of why differences exist and how to rectify them

Disclosure of Interest: None Declared

Elementary mass action stoichiometric simulation models predict non-negligible concentrations of enzyme-bound metabolites

Marta R. A. Matos[*1], Daniel C. Zielinski[2], Lars K. Nielsen[1,3], Nikolaus Sonnenschein[1]
[1]The Novo Nordisk Foundation Center for Biosustainability, Technical University of Denmark, Kgs Lyngby, Denmark, [2]Department of Bioengineering, University of California, San Diego, La Jolla, United States, [3]Australian Institute for Bioengineering and Nanotechnology (AIBN), The University of Queensland, Brisbane, Australia

Your abstract : Improvement of cell factory performance, to the point where production of chosen molecules becomes economically profitable, requires extensive metabolic modification. Metabolic models have been used to both provide new insights into the inner workings of metabolism and new directions for strain engineering. Kinetic models in particular are key to model the dynamics of metabolism and substrate-level enzyme regulation.
Here, we use the elementary Mass Action Stoichiometric Simulation (eMASS) framework to build a prototype kinetic model ensemble for eight enzymes in glycolysis in *E. coli*. Following eMASS, we first build an individual kinetic model for each reaction by decomposing it into elementary reactions, according to the respective reaction mechanism. Next, the associated elementary rate constants are fitted to kinetic data obtained from the literature, e.g. kcat, Km, Ki, while satisfying the respective Haldane relationship. Finally, we assemble the system's kinetic model by combining the individual reaction models and integrating fluxomics and metabolomics data. Since we model both free and enzyme-bound metabolite concentrations explicitly, we drop the common assumption that enzyme-bound metabolite concentrations are negligible ($x_{tot} \approx x_{free}$) and predict the free metabolite concentrations.
Our preliminary results show that the percentage of enzyme-bound metabolite vs. total metabolite can be as high as 40%, i.e. the amount of enzyme-bound metabolite may not be negligible even in glycolysis. These results derive from the fact that in some cases the concentration of metabolites is in the same order of magnitude as the enzymes with which they interact.

Disclosure of Interest: None Declared

Dynamical Modeling of the Immune System in Case of Septicemia

Jean Tallon[1], Françoise Couenne[1], Claire Bordes[1], Fabienne Venet[2], Guillaume monneret[3], Patrice Mony[4], François Guyeffier[4], Virginie Moucadel[5], Melaz Tayakout-Fayolle[* 1]
[1]LAGEPP, [2]Laboratoire d'Immunologie, university of lyon, villeurbanne, [3]Laboratoire d'Immunologie, [4]Service de Pharmacologie Clinique , university of lyon, [5]biomerieux, biomerieux, lyon, France

Secondary topic : Methodological developments for Systems Biology

Your abstract : Homeostasis refers to the ability of a living system to maintain a healthy equilibrium using pro-inflammatory and anti-inflammatory mechanisms despite any change in its environment. Septicemia is the body's response to a generalized infection of the blood by a pathogen. It strongly disturbs the environment of the living system which loses its ability to maintain healthy equilibrium, possibly leading to death or another equilibrium. Sepsis has been recognized as a major public health problem [1].
A study "Sepsis 48h" included twenty-eight patients in septic shock and admitted in two ICUs of a university hospital has been performed. All the clinical characteristics are presented in de [2] . A blood sample was taken every 6 hours for 48 hour, and a sample was taken after 6 days for some patients
In the literature, the modelling of the immune system is quickly limited by the complexity of the systems. The more common models (called pharmacokinetic models) are based on closed and uniform systems and don't take into account thermodynamics or transport phenomena between cells and blood [3].
Our approach considers the environment (open system) and the different subsystems. The immune system is the blood, the subsystems are leukocyte cells and cytokines. The interactions between blood cells, plasma and the environment are described via mass balances. The transport phenomena between cells and blood and thermodynamic equilibrium are considered. The quantities of pro and anti-cytokines are combined to give global information on the inflammatory state of the patient. The proposed dynamic model is strongly nonlinear and it does not come back to initial homeostatic state after septic shock. Several equilibria and limit cycles can be reproduced. This dynamic model can be used to have a better knowledge of septicemia.
From the study « Sepsis 48h", a couple of cytokins ans associated receptors (IL1 and IL10) has been chosen in order to apply the methodology of modelling proposed. The simulation and experimental data of cytokins and receptors evolution have been compared and discussed for the all patients.
[1] Global Sepsis Alliance. WHA Adopts Resolution on Sepsis. https://www.global-sepsis-alliance.org/news/2017/5/26/wha-adopts-resolution-on-sepsis. Accessed 15 Feb 2018.
[2] Cazalis, M.-A. et al. Early and dynamic changes in gene expression in septic shock patients: a genome-wide approach. Intensive Care Med. Exp. 2, (2014)

Disclosure of Interest: None Declared

Predicting Nutritional Uptakes of Bacillus subtilis by Integrating Gene Expression Profiles into Metabolic Constrained-Based Models

Kulwadee Thanamit[*1], Franziska Hoerhold[1,2], Marcus Oswald[1,2], Rainer Koenig[1,2]
[1]Network Modeling, Leibniz Institute for Natural Product Research and Infection Biology (Hans Knoell Institute), [2]Center for Sepsis Control and Care (CSCC), Jena University Hospital, Jena, Germany

Secondary topic : Methodological developments for Systems Biology

Your abstract : Finding drug targets for antimicrobial treatment is a central focus in biomedical research. To discover new drug targets, we are interested in finding out which nutritional needs are important for pathogenic microorganisms in the host or under specific circumstances. Besides this, metabolic fluxes have been successfully constructed and predicted by employing flux balance analysis (FBA) based on constrained based modeling (Orth *et al*., Nat Biotechnol, 2010, Sharma *et al*., Semin Cancer Biol, 2013, Lewis *et al*., Nat Biotechnol, 2010). We develop FBA models using the stoichiometric knowledge of the metabolic reactions of a cell and combine this with experimental data, particularly gene expression profiles. We aim to identify essential drug targets for specific nutritional uptakesof pathogenic microorganisms. As a case study, we implemented our method by using data from *B. subtilis*. We used a metabolic model (Oh *et al*., J Biol Chem, 2007), gene expression data (Nicolas *et al*., Science, 2012), and metabolic flux data from ^{13}C tracing experiments (Chubukov *et al*., Mol Syst Biol, 2013) for validation. The data comprises of fluxes and gene expression profiles of *B.subtilis* grown on 8 different carbon sources. We linearly mapped the expression values to the predicted fluxes as an optimization problem based on mixed-integer linear programming (MIP). A new method was developed to reduce thermodynamically infeasible loops (RED-TIL) to improve prediction results. Validation was performed by comparing predicted flux values with the fluxes from the ^{13}C labelling experiments of the same dataset, and of another, independent dataset (Buescher *et al.*, Science, 2012). By employing our method, our trained model could correctly identify the major carbon sources. We found improved flux predictions when compared to models not employing our new method RED-TIL.

Our approach is promising, it could well predict fluxes in the metabolic network of *B.subtilis*. The concept may suit to predict carbon sources of pathogenic microorganisms and in more complex environments, like e.g. *P.falciparum* in human erythrocytes or Anopheles midgut cells to identify new drug targets.

Disclosure of Interest: None Declared

Modelling the σB mediated stress response in Bacillus subtilis

Torkel Loman[*1], James Locke[1]
[1]UNIVERSITY OF CAMBRIDGE, Cambridge, United Kingdom

Your abstract :
The gram-positive bacteria *Bacillus subtilis* responds to stress in part through the activation of alternative σ factors. For example, the general stress response sigma factor, σB, can be activated by two distinct types of stress, energy and environmental stress. The energy and environmental stress response pathways share a common core, enabling both of them to activate σB. However, the pathways are also partially disjoint where two different mechanisms are used to sense the stress and activate the core pathway. This gives different characteristics to the two stress responses.

The σB response to both energy and environmental stress have been investigated using single cell imaging experiments. This has enabled the discovery that a homogeneous population can exhibit a heterogeneous response to energy stress, but not to environmental stress. When growing on agarose pads, *B. subtilis* responds to energy stress with a stochastic pulsing behaviour where σB activity is randomly turned on and off in each individual bacteria, independently of its activity in other individuals. The response to environmental stress is instead a single activity pulse throughout the population, where σB production is turned on in response to stress and then turned off shortly afterwards, independently of whenever the stress persists.

By utilising that these two pathways are biochemically well characterised we have been able to produce a mathematical model of them, allowing us to simulate the response to various stress inputs and compare to the experimental results. This enables us to explore which features of the energy and environmental stress pathways enables them to generate such distinct behaviours, even though they share a common core. In addition, we have investigated stochastic simulations of our model to determine whenever the inherent stochasticity of the biochemical pathways can be used to explain the heterogeneity observed in the single cell imaging experiments.

Disclosure of Interest: None Declared

WASABI: a dynamic iterative framework for gene regulatory network inference

Arnaud Bonnaffoux[*] [1], Ulysse Herbach[1], Angélique Richard[1], Anissa Guilemin[1], Sandrine Giraud[1], Pierre-Alexis Gros[2], Olivier Gandrillon[1]
[1]ENS LYON / LBMC, [2]cosmotech, lyon, France

Secondary topic : Methodological developments for Systems Biology

Your abstract : Inference of gene regulatory networks from gene expression data has been a long-standing and notoriously difficult task in systems biology. Recently, single-cell transcriptomic data have been massively used for gene regulatory network inference, with both successes and limitations.
In the present work we propose an iterative algorithm called WASABI, dedicated to inferring a causal dynamical network from time-stamped single-cell data, which tackles some of the limitations associated with current approaches.
We first introduce the concept of waves, which posits that the information provided by an external stimulus will affect genes one-by-one through a cascade, like waves spreading through a network. This concept allows us to infer the network one gene at a time, after genes have been ordered regarding their time of regulation.
We then demonstrate the ability of WASABI to correctly infer small networks, which have been simulated *in-silico* using a mechanistic model consisting of coupled piecewise-deterministic Markov processes for the proper description of gene expression at the single-cell level.
We finally apply WASABI on *in-vitro* generated data on an avian model of erythroid differentiation. The structure of the resulting gene regulatory network sheds a fascinating new light on the molecular mechanisms controlling this process. In particular, we find no evidence for hub genes and a much more distributed network structure than expected. Interestingly, we find that a majority of genes are under the direct control of the differentiation-inducing stimulus.
Together, these results demonstrate WASABI versatility and ability to tackle some general gene regulatory networks inference issues. It is our hope that WASABI will prove useful in helping biologists to fully exploit the power of time-stamped single-cell data.

Disclosure of Interest: None Declared

An Alzheimer's landscape: validating cause and effect networks and knowledge discovery on MEDLINE

Jens Dörpinghaus[*] [1] on behalf of Department of Bioinformatics, Alpha Tom Kodamullil[1]
[1]Department of Bioinformatics, FRAUNHOFER INSTITUTE FOR ALGORITHMS AND SCIENTIFIC COMPUTING SCAI DEPARTMENT OF BIOINFORMATICS, Sankt Augustin, Germany

Secondary topic : Methodological developments for Systems Biology

Your abstract : Today the biomedical filed mostly relies on systems biology approaches such as integrative knowledge graphs to decipher mechanism of a disease, by considering system as a whole (holistic approach). In that, disease modeling and pathway databases plays an important role. Knowledge Graphs built using Biological Expression Language (BEL, see www.openbel.org) is widely applied in biomedical domain to convert unstructured textual knowledge into a computable form. The BEL statements that forms knowledge graphs are semantic triples that consist of named entities, functions and relationships (Fluck et al. 2013). We face several challenges while converting knowledge from literature into knowledge graphs. First challenge is dimension reduction, which is building the relevant literature corpora to build the knowledge graphs. It is hard to extract the relevant articles for a topic by an unaided human. Second challenge is the publication bias: biomedical research is biased towards certain well-known findings and it is obvious that you find more articles related to this well-known topic and relatively less number of articles representing novel findings. Apart from the above challenges, knowledge graphs often confronted by various factors such as Completeness, Coverage, Scope and so on.

Here, we propose statistic measures based on document clustering (Dörpinghaus et al. 2017) to quantify completeness and coverage, to prove the quality of a knowledge graph by identifying the scope, to distinguish and prioritize well-known, novel and missing knowledge based on literature. An internal criterion helps to evaluate the model itself and to find the coverage and scope of the knowledge graph. An external criterion is to evaluate the network knowledge against all available scientific knowledge, for example in the entire MEDLINE. While comparing this external criterion with internal criterion, we can define the completeness of the model. This will also quantify the missing knowledge in the network that need to be added to the network. The different network attributes and properties obtained by the external criterion help to distinguishes which topic is overly represented. In addition it gives more information on ‘ignoromes’ – the underrepresented novel findings.

In this poster we will show examples based on our Alzheimer's Knowledge Graph. This network depicts the cause and effect mechanisms around Alzheimer's disease.

Disclosure of Interest: None Declared

Multi-omics - OMIC

Multi-omic pathway enrichment analysis

Jeremie Becker* [1]
[1]BIOASTER, lyon, France

Secondary topic : Methodological developments for Systems Biology

Your abstract : The integration of multiple sources of data presents the advantage of reducing the risk of selecting unreliable information at the single-omics level and increasing the power to discover subtle but coordinated changes. In the present work, the focus is set on transcriptomics and metabolomics data where both data type provide a complementary view about cellular activity. The comparison of molecular profiles across two or more clinical conditions generates large lists of differentially expressed molecules whose interpretation is not straightforward. Researchers are therefore interested in grouping these molecules into functionally homogeneous sets called pathways. While pathway enrichment has become standard in the analysis of single data for over a decade, its application in multi-omics is still in its infancy. To address this challenge, we propose two novel approaches: the first, MOSEA, extends the widely used functional-class-scoring methods GSEA to multi-omics analysis, the second performs over-representation analysis (ORA) based on the Cochran-Mantel-Haenszel (CMH) test. Their performances were compared with existing methods on simulated data and a dataset from Jozefczuk et al. (2010) who investigated the response to heat stress in E. Coli. MOSEA showed both a high specificity and a good ability to reflect synergy across omics in simulations. In addition to the pathways described by Jozefczuk et al., energy-related pathways were also retrieved by the method, in coherence with the stimulation. CMH was, on the other hand, able to detect pathways with a high enrichment in one omics or a moderate to high enrichment in both omics in simulations. Although CMH failed to identify 3 pathways in the biological application, it nevertheless found instances of the 3 main pathway categories described in the original study.

Disclosure of Interest: None Declared

A design principle of GPCR signaling through beta-arrestins

Nathalie Langonné[1], Franck Vandermoere[2], Thomas Bourquard[1], Elisabeth Cassier[3], Christophe Gauthier[1], Thomas Boulo[1], Anne Poupon[4], Pascale Crépieux[* 4], Philippe MARIN[2], Eric Reiter[1]

[1]INRA, Nouzilly, [2]IGF, [3]CNRS, Montpellier, [4]CNRS, Nouzilly, France

Secondary topic : Modelling Networks and Circuits

Your abstract : G protein-coupled receptors (GPCRs) are transmembrane proteins devoted to the integration of extracellular stimuli into appropriate cellular outcomes. To do so, they regulate intracellular signaling pathways leading to gene expression. In addition to G proteins, β-arrestins are adaptor proteins that spatially and temporally regulate GPCR activity. So far, it is not known whether the coordinated action of β-arrestins differs between distinct GPCRs, at the cell systems level. To address this question, we performed large-scale transcriptomic and quantitative proteomic analyses. 5HT2C, 5HT4a and FSH receptors were transiently expressed in HEK293 cells and endogenous β-arrestin expression was silenced using siRNA in order to: ***i)*identify genes/proteins regulated by β-arrestins; *ii)*determine which targets are receptor-specific and which (if any) are generic, and *iii)*infer β-arrestin-dependent networks.**

Quantitative phosphoproteomics revealed that β-arrestin-dependent phosphorylation events represented about 20% of the phosphoproteome regulated by agonist stimulation of each receptor. A high degree of redundancy was observed in the phosphoproteomes under the control of the three receptors. However, at the transcriptomic level, redundancy was less pronounced, suggesting that common signaling pathways regulate distinct sets of genes upon engagement by different GPCRs. Interestingly, FSH and 5HT2C receptors, that both activate ERK1,2 MAP kinases *via*β-arrestins, shared more β-arrestin-dependent genes, compared with 5HT4a-receptor. Conversely, FSH and 5HT4a receptors, that are coupled to Gαs, exhibited more common G-dependent genes, compared to the Gq-coupled 5HT2C receptor. β-arrestin-dependent signaling networks for each receptor were inferred from phosphoproteomics data, using Ingenuity® Pathway Analysis. Transcriptional regulators were highly connected to corresponding b-arrestin-dependent genes. The specificity of these connections for each receptor was established by challenging 30 independent random lists of transcriptional regulators for their connectivity with β-arrestin-dependent genes.

In conclusion, we inferred β-arrestin-dependent signaling and gene networks for three distinct GPCRs coupled to distinct G proteins. Comparing results from β-arrestin-binding GPCRs coupled to distinct G proteins highlighted a minimal "β-arrestin signature", that may be considered as a design principle of GPCR signaling through highly versatile and adaptative β-arrestins.

Disclosure of Interest: None Declared

Cell lines vs tissue - a comparative study of gene expression using FunHoP

Kjersti Rise[*1], Finn Drabløs[2], Morten Beck Rye[2,3]
[1]Department for Clinical and Molecular Medicine, [2]Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, [3]Clinic of Surgery, St. Olavs Hospital, Trondheim, Norway

Secondary topic : Modelling Networks and Circuits

Your abstract : Since the first cell lines were cultivated, the development, knowledge, and usage of cell lines has grown into a solid position in basic research. Cell lines allows studies of multiple tissue types, including complex tissues where *in vivo* studies would be difficult. However, as recreating the natural environment in a flask is close to impossible, growing cells *in vitro* means that the complex signaling system surrounding the cell is lost. Studies performed on cell lines will therefore not necessarily have the same outcome as studies performed *in vivo* (if such studies could be performed). In order to examine the similarities and differences between cell lines and tissue, we compared RNA-sequencing data of different cell lines and tissue in a prostate cancer cohort. We used three cancer cell lines: DU145 (hormone insensitive), LNCaP (ERG negative, AR responsive), and VCaP (ERG positive, AR responsive), and two normal cell lines: RWPE and PrEC, along with normal and cancerous tissue samples. Differential expression was calculated on all 16 combinations of cell lines and tissue. The resulting lists of up- or down-regulated genes were analyzed by DAVID, finding the corresponding functional categories. Highest ranked categories, as well as repeating patterns of categories among the combinations, were further used as basis for pathway analysis. In this study we use our newly developed pathway analysis method FunHoP, which enhances visualisation and analysis of biological pathways by combining read counts from RNA-sequencing with pathways from KEGG. As FunHoP includes all functional homologs and prioritizes genes based on read counts, the pathways become more reliable and biologically relevant than conventional pathway studies, and can reveal more differences or similarities between tissue and cell lines. The aim of the study is to use FunHoP in order to get new insight to which pathways are regulated differently or similarly between cell lines and tissue.

Disclosure of Interest: None Declared

Integrative multi-omics approach to identify the factors responsible for PARPi resistance in BRCA1-deficient breast cancers

Jinhyuk Bhin[*1]
[1]Netherlands Cancer Institute, Amsterdam, Netherlands

Secondary topic : Multi-omics

Your abstract : BRCA1 is one of the most popular tumor suppressor genes whose mutations are highly liked to cancer risk, especially for breast and ovarian cancers. While 12% of total women develop breast cancer during their lifetime, 72% of women inheriting harmful BRCA1 mutation develop breast cancer. Not only for increasing cancer risk, BRCA1 mutations are also associated with poor survival of patients and high risk of developing new primary tumor in opposite breast.

Due to crucial functions of BRCA1 in DNA damage response and DNA integrity, loss of BRCA1 function leads to genomic instability which is hallmark of cancer. Paradoxically, impaired DNA repair capacity in BRCA1-deficient tumors also give a chance to treat this type of cancer by inducing high burden of DNA damage which leads to cell death. PARP inhibitor (PARPi) is one of the promising drugs for treatment of BRCA1-deficient tumors through synthetic lethality that simultaneous inhibition of BRCA1 and PARP leads to cell death [4]. Unfortunately, like other cancer treatment, PARPi treatment to BRCA1-deficient tumors eventually give rise to resistance and it makes. Therefore, understanding of underlying resistance mechanisms is crucial step for improvement of clinical implication of PARPi.

In this study, using K14cre;Brca1$^{F/F}$;Trp53$^{F/F}$ (KB1P) mouse, we systematically analyzed molecular characteristics of BRCA1-deficient tumors before and after acquiring PARPi resistance. Through proteogenomic approach based on genomic and proteomic data, we provided comprehensive view of molecular basis that underlies PARPi resistance. Interestingly, resistant tumors tend to have high mRNA-protein correlations for the genes involved in DNA damage response pathway while sensitive tumors don't. Also, resistant tumors harboured distinct mutation profiles each other suggesting that each resistant tumor acquired resistance by distinct genomic evolution in response to PARPi. Also, proteomic profiles of resistant tumors defined several key signaling pathways involved in DNA repair pathways which couldn't defined by genomic analysis. Our Integrative proteogenomic approach provides novel insights for PARPi resistance in BRCA1-deficient tumors which can be valuable resources for therapeutic strategy development.

Disclosure of Interest: None Declared

Highlighting the condition-specific protein-protein interaction by integrating expression data into the interactome network: a case of AGPase protein.

Treenut Saithong[*] [1, 2], Ratana Thanasomboon[3], Saowalak Kalapanulak[1, 2], Supatcharee Netrphan[4], Malinee Suksangpanomrung[4]

[1]Bioinformatics and Systems Biology Program, School of Bioresources and Technology, [2]Systems Biology and Bioinformatics Research Group, Pilot Plant Development and Training Institute, [3]Biological Engineering Program, Faculty of Engineering, King Mongkut's University of Technology Thonburi, Bangkok, [4]National Center for Genetic Engineering and Biotechnology (BIOTEC), National Science and Technology Development Agency (NSTDA), PathumThani, Thailand

Secondary topic : Multi-omics

Your abstract : Protein-protein interaction (PPI) is referred to the association of proteins in cells. It is a temporal state of proteins and typically provides a mean of proteins to function in the cellular regulatory network, both in terms of time and space. Such interaction promptly happens and only stays in short period, so that is not easy to be captured and traced. The large-scale PPI studies are, thus, conducted based upon computational prediction whereby all possible interactions are proposed to protein pairs according to conserved domains, prior knowledge of the homologous proteins, or the clues on their thermodynamic properties. The resulting interactome networks are effective to provide the list of potential associated proteins, but lack of information on conditions of when and where the interactions occur as well as the conveying function. To infer PPIs in a specific condition, multi-omic expression data were integrated into the interactome network to highlight the putative PPIs happened in the observed conditions. The rationale was applied to study the associated enzyme subunits of ADP-glucose pyrophosphorylase (AGPase) proteins that are specific to metabolism in leaves and roots of cassava. AGPase is an important enzyme in starch biosynthesis pathway. Generally, small catalytic subunits (APS1 and APS2) and large regulatory subunits (APL1, APL2, and APL3) need to be associated to allow a normal function of AGPase enzyme in the metabolism. Incorporating transcriptome data measured from cassava leaves and root tissues (SRR3629818, SRR3629835, SRR3629853, SRR3629825 and SRR3629843) into the MePPI-In, the interactome network of cassava proposed by Thanasomboon *et al* (2017), suggested that the function of AGPase in these tissues may be driven by distinct associated enzyme subunits. APS1-APL3 was found to be the predominant associated subunits in roots, whereas APS1-APL1 was likely to be the association responsible to the AGPase function in leaves metabolism. Our study showed that integration of expression data into the interactome network could gain more insight into the condition-specific protein-protein interaction.

Disclosure of Interest: None Declared

Transomics: integrated analysis through multiple molecular layers

Fumiko Matsuzaki[*1], Shinsuke Uda[1], Yukiyo Yamauchi[1], Hiroyuki Kubota[1]
[1]Medical Institute of Bioregulation, KYUSHU UNIVERSITY, Fukuoka, Japan

Secondary topic : Methodological developments for Systems Biology

Your abstract : Advances in omics technologies have enabled us to measure a large number and variety of molecular components of cells. The effective combination of multi-omics data should enormously assist in our understanding of complex biological phenomena. However, in addition to each omics datum having different integrity and biological and technical variations due to the peculiar chemical properties and biological functions of the involved molecules, another problem is the difficulty of data integration. A need exists for proper measurements to be performed on each molecular layer as well as an analytic methodology to deal with the differences in data quality and molecular function.

In order to establish a practical framework to integrate large scale multi-omics data, we set our focus on the analysis of insulin action on metabolism and other biological processes in mouse liver as a pilot study and performed transcriptomics, expression proteomics, phosphoproteomics and metabolomics with time series of tissue samples obtained during a period of four hours after insulin treatment. We then set up procedures ranging from data cleaning, identity conversion and matching among different omics data sets, to visualization on pathway maps so as to examine tendencies of sets of omics data and their interactions with biological processes. With the use of the processed data we built ordinary differential equation models to analyze the dynamic characteristics of protein expression and phosphorylation and metabolite pool concentration. We expect that the series of automated processes for a quantitatively integrated approach with multi-omics data, which we call transomics, will accelerate comprehensive understanding of how the molecular networks of various biological systems are regulated through the coordination of different molecular layers and expand the foundations of modern biology.

Disclosure of Interest: None Declared

Integrated omics analysis for assessing the biological impact of repeated whole cigarette smoke exposure on a 3D bronchial tissue culture

Kazushi Matsumura[*1], Shinkichi Ishikawa[1], Nobumasa Kitamura[1], Yuichiro Takanami[1], Shigeaki Ito[1]
[1]Scientific Product Assessment Center, JAPAN TOBACCO INC., Yokohama, Japan

Secondary topic : Multiscale Systems Biology

Your abstract : Cigarette smoke (CS) is considered to be a risk factor for inflammatory lung diseases. The human lung epithelium acts as a barrier to inhaled exogenous chemicals, and the respiratory tract in individuals with inflammatory lung disease shows abnormal tissue morphology and functions, including goblet cell hyperplasia and mucus hypersecretion. Although in vivo animal inhalation studies have been used to reproduce the pathogenesis of lung diseases, they are limited by interspecies differences, and studies using three-dimensional (3D) culture models of human bronchial tissue have been used to overcome this limitation. We previously conducted CS-exposure experiments using a 3D co-culture model of human bronchial tissue with a collagen-embedded fibroblast layer beneath the fully differentiated epithelial layer. Secretion of several cytokines increased with repeated CS exposure over a 2-week period, suggesting that even low levels of CS could exert cumulative cellular effects and repeated CS exposure could lead to chronic inflammation.
The present study aimed to determine the biological impact of chronic CS exposure on human bronchial tissue using a 3D co-culture model. The 3D bronchial tissue culture was exposed to whole CS for 2 weeks to induce continual inflammation, and changes in biological processes were comprehensively investigated by metabolomic, transcriptomic, and proteomic analyses. These integrated analyses indicated that repeated CS exposure impaired energy production-related pathways. We further investigated the key regulators governing the observed CS-induced changes by examining upstream regulators. Epidermal growth factor receptor (EGFR), which is known to induce goblet cell hyperplasia and mucus hypersecretion, was identified as a potential key upstream regulator. We therefore also examined changes in protein expression in the apical surface liquid of the 3D cultures, and showed that several biomarkers of lung diseases (e.g., mucin 5AC, and matrix metalloproteinases 1 and 9) were increased by CS exposure. Overall, these findings suggest that repeated CS exposure led to metabolic disruption and alterations in the expression profiles of genes related to EGFR activation. Moreover, CS-exposed tissues secreted biomarkers of lung diseases, suggesting that the 3D bronchial tissue cultures were able to exhibit specific disease symptoms.

Disclosure of Interest: None Declared

EpiMOLAS: a web-based system for genome-wide DNA methylation analysis

Sheng-Yao Su[1], Shu-Hwa Chen[1], Yi-Hsun Lu[1], Chung-Yen Lin[* 1]
[1]INSTITUTE OF INFORMATION SCIENCE, ACADEMIA SINICA, Taipei, Taiwan

Secondary topic : Multiscale Systems Biology
Your abstract : Abstract

Summary
DNA methylation is a crucial epigenomic mechanism involved in various biological processes, regulating gene expression and chromatin dynamics. Using whole-genome bisulfite sequencing (WGBS) approach or other modified protocols, various types of cytosine modification state can be revealed at the single nucleotide level. However, the WGBS data analysis process is usually complicated and challenging. To alleviate the analytic difficulties, we integrated multiple data processing steps and the downstream analysis into a two-phase system. First, we developed a Galaxy workflow, calculating the methylation level from raw data to a tab-delimited methylation table, and wrapped it as a Docker image DocMethyl. Using this Docker image, users can rapidly deploy an executable environment and process their data via Galaxy's web interface. Next, the summarized methylation table can be uploaded to web-based system EpiMOLAS for versatile WGBS in-depth analysis and visualization under different experiments and research scenarios. Currently, available reference genomes in DocMethyl and EpiMOLAS include human (GRCh37/hg19, GRCh38/hg38), mouse (GRCm38/mm10) and Arabidopsis (TAIR10).

Availability and implementation

1. The Galaxy Docker image DocMethyl is available at https://hub.docker.com/r/lsbnb/galaxy-epimolas-pe/
2. EpiMOLAS is publicly accessible at http://symbiosis.iis.sinica.edu.tw/epimolas/

Disclosure of Interest: None Declared

Differential proteomics reveals sulfur source-dependent physiological adaptations in the fuel biodesulfurizing Rhodococcus sp. IGTS8

Christine Carapito[1], Aurelie Hirschler[1], Valérie Cognat[2], Vartul Sangal[3], Ashraf El Nayal[4], Malek Alioua[2], Alain Van Dorsselaer[1], Dimitri Heintz[2], Huda Mahmoud[5], Wael Ismail[* 4]

[1]Laboratoire de Spectrométrie de Masse Bio-organique, Institut Pluridisciplinaire Hubert Curien, UMR7178 CNRS-Université de Strasbourg, 25 rue Becquerel, [2]Institut de Biologie Moléculaire des Plantes, CNRS UDS UPR2357–Université de Strasbourg, Strasbourg, France, [3]Faculty of Health and Life Sciences, Northumbria University, Newcastle upon Tyne NE1 8ST, Newcastle upon Tyne , United Kingdom, [4]Environmental Biotechnology Program, Life Sciences Department, College of Graduate Studies, Arabian Gulf University, Manama, Bahrain, [5]Department of Biological Sciences, College of Science. Kuwait University, Kuwait, Kuwait

Secondary topic : Systems Biology for Synthetic Biology

Your abstract : Microbial biodesulfurization of fossil fuels is a green approach for the production of ultra-low sulfur transportation fuels such as diesel. We investigated the proteome of the model Actinobacterium *Rhodococcus* sp. IGTS8, which is capable of growing in mineral salts medium containing either $MgSO_4$ or dibenzothiophene (DBT, a model organosulfur compound for biodesulfurization research) as a sole sulfur source. Both the total proteome and secretome were analyzed in samples collected during the early-, mid-, late-log and stationary phases. Initial analyses revealed differential expression of a large number of proteins that were upregulated or down regulated depending on the type of the sulfur source. In addition, several proteins were exclusively observed in cultures grown in medium containing either DBT or $MgSO_4$. Here we focus on this second category. These proteins were detected in the four growth phases. The number of the proteins was always much higher in the DBT culture, where it increased with the incubation time, and the largest number was detected in the stationary phase cells (85 unique proteins). The majority of the proteins specific to the $MgSO_4$ cultures were associated with transport of metabolites and oxidoreductase activity. In the DBT cultures, the detected proteins were more functionally diverse and covered sulfur metabolism, sulfate starvation, sulfur acquisition, redox reactions, stress response, nucleic acids processing and nucleotide metabolism, solute transport (mainly ABC-type), regulation of gene expression (including two-component systems), metabolism of sugar, lipids, and amino acids, chaperones, biosynthesis of enzyme cofactors, biosynthesis of osmoprotectants, oxidative phosphorylation, cell envelope biosynthesis, cell division, iron uptake, metal homeostasis, and mycothiol biosynthesis. Interestingly, the DBT-grown cells recruited proteins encoded by plasmid-born genes during the four growth phases, while no plasmid-encoded proteins were detected in the $MgSO_4$ cultures. While many proteins were detected over several growth phases, a few proteins were growth phase-specific. In conclusion, the type of the sulfur source had a profound impact on the proteome of the IGTS8 cells. The DBT-grown cells exhibited a massive physiological and metabolic response to cope with the stressful condition of low sulfur availability due to the strong hydrophobicity of DBT.

Disclosure of Interest: None Declared

Genome-wide two-step pre-mRNA splicing kinetics in human cells

Leonhard Wachutka[* 1], Livia Caizzi[2], Patrick Cramer[2], Julien Gagneur[1] on behalf of I12G and I12G - Gagneurlab
[1]Computational Biology, TUM, Garching, [2]Molecular Biology, Max Planck Institute for Biophysical Chemistry, Goettingen, Germany

Secondary topic : Systems Biomechanics
Your abstract : Although extensive *in vitro* studies have strongly advanced our understanding of the splicing process, *in vivo* kinetics of individual steps of splicing and how these are controlled by regulatory elements remain far less understood. We had developed transient transcriptome sequencing (TT-Seq), a labelled RNA sequencing protocol which, by the use of an early RNA fragmentation step [1], enables quantification of human RNA metabolism at the resolution of individual phosphodiester bonds [2]. Here, using deeply sequenced TT-seq data at labeling durations ranging from 2 to 30 minutes in K562 cells, we untangled and quantified for the first time the rates of disappearance of splice donor and splice acceptor sites genome-wide. We find that the disappearance rate of the donor site, reflecting kinetics of the first catalytic step, but not of the acceptor site, reflecting kinetics of the second catalytic step, is limited by polymerase elongation for long intron. Moreover, we derived computational models that can predict these rates at a median relative error smaller than two-fold from sequence alone, while these rates span 2 orders of magnitude. Effects or lack thereof of individual nucleotides predicted by these models agree well with contacts between the spliceosome and the precursor RNA according to existing secondary structure (first catalytic step) and predict further contacts for structures yet to be obtained (second catalytic step). Furthermore, our model revealed *de novo* sequence motifs predictive for these rates matching binding sites of splicing factors and novel, yet to be characterized motifs.
We also introduced a novel quantity, splicing yield, which we define as the proportion of precursor RNA successfully converted into spliced RNA, and which we quantified genome-wide thanks to our data. Although the minor spliceosome takes 3 times more time to splice than the major spliceosome, surprisingly both showed similar splicing yields. In contrast long non coding RNAs showed longer splicing times and lower yield than coding RNAs.
Altogether, our study provides an unprecedented detailed dissection of splicing kinetics genome-wide and yield novel insights into its genetic determinants in the human genome.

[1] Schwalb, B. et al., 2016. TT-seq maps the human transient transcriptome. Science (New York, N.Y.)
[2] Wachutka, L. & Gagneur, J., 2017. Measures of RNA metabolism rates: Toward a definition at the level of single bonds. Transcription

Disclosure of Interest: L. Wachutka: None Declared, L. Caizzi: None Declared, P. Cramer: None Declared, J. Gagneur Conflict with: In selection comitee

Epigenetic landscape of low versus high-order chromatin folding

David Fournier[*1], Susanne Gerber[1] and Computational Systems Genetics group
[1]Institut für Enwicklungsbiologie und Neurobiologie, Johannes Gutenberg-Universitaet, Mainz, Germany

Your abstract : Epigenetics refers to a complex set of regulatory mechanisms which combine with the genetic sequence to generate phenotypic features like eye color or height. The term "epigenetics" involves very different kinds of features such transcription factors binding, histone modifications or repair machineries, among many others. These different features can be viewed in a broad sense as acting in combinations in order to change the expression of a given gene or to change the structure of the DNA. For instance, the presence of certain modifications of histones (the most abundant proteins of the nucleus that help folding the DNA) and a given transcription factor together with the polymerase II will lead to the expression of a certain gene, while another sets of epigenetic features, including other histone modifications, will lead to its repression.
I am currently testing which combinations of different epigenetic features (factors, modifications of histones, DNA methylation and accessibility) matter for transcription and chromatin folding. These associations are helpful to generate basic rules such as "presence of enzyme E and modifications Mi lead to expression of gene G". I studied these epigenetic associations and their relation to genome folding by integrating data from ChIP-seq (a method to probe protein-DNA interactions) and Hi-C (which list contacts between DNA regions). Using canonical correlations and Boolean models, I could find specific epigenetic rules that are associated to genome folding at short and long-distance. I could show that a combinatorial epigenetic regulatory signal is associated to 1Mb-distant interactions, related to gene regulatory mechanisms, while extremely distant interactions are more favorably associated with chromosome large-scale packing, such as CTCF or SMC3. Furthermore, a theoretical model will be proposed to visualize these different constraints in a 3D environment.

Disclosure of Interest: None Declared

Elucidating genetic control of metabolic networks under different dietary conditions

Valentina Klaus[*1], Sonja C Schriever[1], Paul T Pfluger[1], Dominik Lutter[1]
[1]Institute for diabetes and obesity, HELMHOLTZ CENTER MUNICH, München, Germany

Your abstract : Metabolites are an important readout of cells and tissues. Genetic control of metabolic pathways, their dynamics, and dependence on different diets or diseases remains rather unknown. Thus, integration of transcriptional and metabolomics data, is a key to further dissect and identify gene to metabolite interactions.
An example for an imbalanced metabolic system induced by diet is hepatic steatosis. Hepatic steatosis, or fatty liver, can accompany obesity, which adds another burden, aside from the elevated risk of diabetes, on the health of obese individuals, especially if it progresses to cirrhosis and liver failure. Therefore, identifying genes involved in liver steatosis development would help to find therapeutic approaches to treat that comorbidity.

In our approach we utilize partial correlations to estimate genetic impact on pairwise metabolite correlation. We generate a weighted and colored graph where nodes are formed by metabolites and genes set up the edges. Thereby, several genes can connect more than two metabolites and a pair of metabolites might also be connected by more than one gene. This graph can be interpreted as a hypergraph or bipartite graph that allows us to uncover novel relations between gene expression and metabolic reactions. Furthermore, by generating multiple graphs depending on different dietary conditions we are able to compare their topologies and identify the genetic impact on the regulation of metabolic pathways.

We applied our method on microarray data and metabolite concentrations of metabolites involved in metabolic diseases measured in livers of healthy chow and high fat diet (HFD) fed mice that usually show a liver steatosis phenotype. We observe genes that are enriched in one specific region of the graph, which indicates direct gene interactions within a densly connected subgraph of our metabolite network. Thus we are able to identify genes potentially susceptible for drug treatment or might function as indicator genes for a developing hepatic steatosis.

Disclosure of Interest: None Declared

Role of DNMT3B and hnRNPH in regulation of exons embedded in GC-rich introns

Sebastien Lemaire[*1], Louis DULAURIER[1], Hélène POLVECHE[1], Didier AUBOEUF[1]
[1]LBMC, ENS de Lyon, LYON, France

Your abstract : Alternative splicing affects 95% of the human genes. It is an important process in the regulation of gene expression, and a large number of exons is mis-spliced in diseases such as cancer. Splicing is co-transcriptional and therefore chromatin remodeling and splicing functionally interact, tuning each other. Until now, studies investigating this crosstalk depicted genome-wide correlations or mechanisms of particular cases but they are not sufficient to provide general rules. We investigated this question by analyzing the effect of the siRNA-mediated depletion of several chromatin factors on the splicing outcome by RNA-sequencing in mammary epithelial cells (MCF-7). This analysis identified in particular 571 exons whose inclusion is dependent on the presence of the DNA methyl-tranferase DNMT3B, hence associating their splicing regulation to DNA methylation. DNMT3B is of great interest as it is depleted in cells more advanced in epithelio-mesenchymal transition such as the MDA-MB-231 cells. These cells also lack DNA methylation around the DNMT3B-regulated exons and the DNMT3B-regulated exons are also mis-spliced compared to the MCF-7 cells. By characterizing the genomic features of the DNMT3B-regulated exons, we observed that they are surrounded by short flanking introns and that they are in GC-rich regions, which can fold into highly stable hairpins according to free energy. Moreover, we detected by PCR that the loss of DNMT3B increases the mis-splicing of the flanking introns. This suggests that the inclusion of the DNMT3B-regulated exons depends on the definition of their flanking introns. Strikingly, the intronic regions closed to the splicing sites are enriched for G-triplets, which are intronic splicing enhancers that can be recognized by the splicing factor hnRNPH. In accordance to this observation, depletion of hnRNPH by siRNA also affects the splicing outcome of the DNMT3B-regulated exons. Taken together, these results suggest that the flanking introns of the DNMT3B-regulated exons are defined by hnRNPH. Structural studies support that hnRNPH would fold the intron through its binding of the G-triplets, bringing the splicing sites closer for proper intron processing. In absence of DNMT3B, the intron would be misfolded, preventing the splicing sites to reach each other, thus resulting in the skipping of the exon.

Disclosure of Interest: None Declared

Deciphering transcriptional and epigenetic remodeling of actin dependent genes during neuronal diseases

Kanak Mungikar[*1], Marianne Müller[2], Susanne Gerber[1]
[1]Faculty of Biology, Institute for Developmental Biology and Neurobiology and Center for Computational Sciences in Mainz, JOHANNES GUTENBERG UNIVERSITY, MAINZ, [2]Translational Psychiatry, Department of Psychiatry and Psychotherapy & Focus Program Translational Neuroscience (FTN), Johannes Gutenberg University Medical Center, Mainz, Germany

Your abstract : Actin cytoskeleton plays an important role in neuronal development and its diseases by contributing in the regulation of cellular processes like cell shape, migration, maintenance of cell junctions etc. Dendritic spines are involved in synaptic transmission and rich in actin filaments. Malfunction of actin can affect shape and size of dendritic spines which subsequently may result to neuronal diseases. Previous studies provided evidences of dysfunction in actin cytoskeleton also strongly contributes to the development of neurodegenerative diseases such as Alzheimer's disease. Despite decades of research and progress over understanding the molecular and cellular aspects behind actin related genes underlying neuronal diseases, very little is known about their transcriptional and epigenetic mechanisms.

In line with this, we explored several publicly available transcriptomics and epigenomics datasets for neuronal diseases like autism, Alzheimer's, Parkinson's, etc. using an integrative analysis approach. We could show that transcriptomics and epigenomics (like DNA methylation, chromatin openness and histone modification) feature analysis of actin related genes reveals a specific gene expression pattern for diseased and healthy states. Upon exploring gene regulatory network through combinatorial analysis, certain sets of transcription factors regulating actin related genes were found to be enriched. Implementation of machine learning methods helped us to improve the prediction of transcription factors regulating actin related genes.

I would like to present these results. We also planned to implement validation strategies such as (i) in-vivo overexpression and knockout studies of certain predicted transcription factors regulating these genes using mouse models as well as (ii) behavioral studies. Altogether, our findings reveal gene regulatory network using multi-omics measurements of actin related genes by deciphering transcriptional and epigenetic remodeling critical for neuronal diseases.

Keywords: Actin, neuronal diseases, machine learning, gene regulation

Disclosure of Interest: None Declared

Identification of target genes and signaling networks of Wnt11 in human breast cancer progression

Maren Sitte[*1], Kerstin Menck[2], Willy Pfützenreuter[2], Antonia Schubert[2], Michaela Bayerlová[1], Claudia Binder[2], Tim Beißbarth[1], Annalen Bleckmann[2]
[1]Dept. of Medical Statistics, [2]Dept. of Hematology/Medical Oncology, University Medical Center Göttingen, Göttingen, Germany

Your abstract : The non-canonical Wnt protein Wnt11 is known to be overexpressed in many human cancers including human breast cancer. While Wnt11 overexpression is associated with increased tumor cell migration and invasion, the molecular mechanisms underlying these effects are largely unknown. Therefore, we aimed to identify the cellular signaling network and target genes of Wnt11 that are involved in Wnt11-induced breast cancer invasion.
We first created human MCF-7 breast cancer cells stably overexpressing Wnt11 and characterized the cells by RNA-sequencing. The analysis revealed 42 genes that were significantly differentially expressed in Wnt11-positive cells, many of them involved in cell adhesion. In order to identify signaling molecules involved in Wnt11 signal transduction, we stimulated MCF-7 cells with recombinant Wnt11, performed a reverse phase protein array (RPPA) and set up network models using a bioinformatics approach. To reconstruct the pathways of the measured proteins in the RPPA we applied the method DDEPN and used pwOmics as a integrative approach to generate a network estimated from both data sets. Thereby, we identified a subset of proteins that was phosphorylated after 5-10 minutes of Wnt11 stimulation. To validate the results, we performed Western Blots which confirmed the activation of Akt in Wnt11-stimulated cells. Inhibition of the PI3K-Akt pathway, using specific inhibitors that are also in clinical use, resulted in a reduction of the pro-invasive effect of Wnt11 on breast cancer cell invasion.
Taken together, our analyses shed light on Wnt11-induced signaling pathways involved in breast cancer progression that could be used as targets for therapy.

Disclosure of Interest: None Declared

Protein-Protein Interaction (PPI) network analysis for Salmonella infected cells

Jens Rieser[*1], Jörg Ackermann[1], Ina Koch[1]
[1]Molecular Bioinformatics, Institute of Computer Science, Johann Wolfgang Goethe-University, Frankfurt am Main, Germany

Your abstract : Salmonella typhimurium provokes gastroenteritis and typhoid fever and causes many thousands death every year. The post-translational modification of proteins after an infection is of major interest. Ubiquitination and phosphorylation are two reversible possibilities for a quick answer of the cell to environmental changes. Phosphorylation is known for activation of several protein cascades and ubiquitination builds a dense coat around cytosolic Salmonella cells [1].
To investigate the differences and similarities between ubiquitination and phosphorylation of proteins during a Salmonella infection, we analyzed the data of two different datasets, one of changes in expression levels of phosphorylated proteins in Salmonella-infected and uninfected cells [2] and the other of changes in ubiquitinated proteins [3]. We used the proteins of the two datasets to compile PPI in three databases, STRING, IntAct and BioGRID, taking into consideration the different scoring of PPI in each database. The final network was created in Cytoscape with 1,704 proteins and 18,974 interactions.
Based on the network topology, we clustered the derived PPI network into functional groups according to their interactions applying the Girvan-Newman algorithm. For each cluster we performed a GO- and Pathway-analysis to determine the biological function. Complexes and strongly interacting subnetworks were found by computing cliques. Here we show different possibilities to analyze host PPI and get better insight into the modification of proteins during a Salmonella infection. For example, HOIL1 is clustered in a group of 60 proteins, from which 27 have the GO-term 'protein ubiquitination'. In the GO clustering on the other side, it can be assigned to 'positive regulation of apoptotic signaling pathway' with a group of 31 proteins with only 35 edges, containing completey different proteins than the topological clustering. Interestingly, in both subnetworks a sixth of the proteins is only phosphorylated proteins, indicating that HOIL1 interacts mostly with ubiquitinated proteins.
[1] Stolz, A., et al. Nature Cell Biology 16.6 (2014):495-501
[2] Rogers, L. D., et al. Science Signal. 4.191 (2011): rs9-rs9
[3] Fiskin, E., et al. Molecular Cell 62.6 (2016) 967-981

Disclosure of Interest: None Declared

Latent linkage highlights strong relations between DNA polymorphisms and the chromatin structure

Susanne Gerber[*1], David Fournier[2], Charlotte Hewel[2], Illia Horenko[3]
[1]Faculty of Biology, Johannes Gutenberg University of Mainz, [2]Faculty of Biology , Johannes Gutenberg University Mainz, Mainz, Germany, [3]Faculty of Informatics, Universita della svizzera italiana, Lugano, Switzerland

Secondary topic : Methodological developments for Systems Biology

Your abstract : Understanding an impact of the genome sequence on the 3D structure and folding of DNA is one of the core topics in biomedical research. On the small-scale atomistic level this understanding can be gained applying efficient computational tools from molecular dynamics. However, on the large-scale genome level, popular genomic analysis methods reveal no apparent relations between the genomic and the 3D steric DNA informations. We provide evidence indicating that this can be explained by the significant role of latent impacts. Deploying the common tools of latent model inference from machine learning for the considered human datasets we show existence of a statistically-significant strong connection between the pairwise relations among Single Nucleotide Polymorphisms (SNP, being point mutations in the DNA sequence) and the pairwise DNA contact probabilities (captured by the steric Hi-C measure). The identified connections are robust with respect to the choice of the sequencing platform and reveal latent 3D steric effects within the 1D SNP data, best reflected by the chromatin loops in the fractal globule packing captured by high resolution Hi-C maps.
We will provide evidences indicating that ignoring latent impacts in common relation measures computations (e.g., when computing standard linkage disequilibrium and cross correlation measures) - as well as the mathematical-inappropriateness of commonly-used linear correlation analysis in evaluating relations between the probability measures – are among the main reasons why these strong relations were “invisible” to the conventional statistical tools used in the modern genomics and genetics.

Disclosure of Interest: None Declared

Multi-Omic Characterisation of Bladder and Lung Carcinomas using a Novel Scanning Quadrupole DIA Acquisition Method

Adam King[*1], Lee Gethings[1], Robert Plumb[2]
[1]WATERS CORPORATION, Wilmslow, United Kingdom, [2]WATERS CORPORATION, Milford, United States

Your abstract : Introduction

Cancer is a complex and life threatening disease, existing in many forms which have unknown pathogenesis. A combination of genetic and lifestyle factors such as smoking are known to contribute towards both lung and bladder cancer, with lung cancer providing over 230,000 diagnosed cases in the United States annually. The exact mechanisms of carcinoma development during various stages are still not well understood. Here, we describe a multi-omic approach, combining lipidomic, metabolomic and proteomic approaches, to reveal molecular factors that may be involved in these biomolecular processes.

Methods

Plasma samples from three biological states (control, bladder and lung carcinoma) were used with each group consisting of plasma from six individuals. Samples were prepared using previously described techniques to provide protein, metabolite and lipid extracts, with the proteins being reduced, alkylated and tryptically digested. In all cases, samples were LC separated and data acquired using a DIA method (SONAR), whereby the quadrupole (MS1) was continuously scanned between *m/z* 50-600 (metabolites) and 400-900 (lipids/peptides). A quadrupole transmission width of 10 Da and 20 Da were employed for lipidomic/metabolomic and proteomic analyses respectively.

Results

LC-MS data were acquired in positive and negative ion electrospray mode with an oa-QTof platform utilizing a broadband acquisition technique (SONAR) data independent acquisition workflow. Progenesis QI (and QIP for proteomics) was utilised for data processing to provide normalised values prior to statistical analysis. Principle component analysis of the lipids showed clear distinction between groups and OPLS-DA was used to determine features of significance prior to identification using databases. SONAR-based analysis indicates that the scanning quadrupole enables over an order of magnitude more specificity than a static quadrupole operated with the same resolution.

Proteomic data were searched against a Uniprot *Homo sapien* database limited to 1% FDR, against a spectral library using Spectronaut and comparatively analysed the results from both workflows. A number of significant proteins involved in antigen and lipid binding were exhibited and biological significance of the results was established by merging data from all omic experiments. Pathway analysis identified significant pathways including complement activation, B cell mediated immunity and receptor signalling as key.

Disclosure of Interest: None Declared

Studying the effect of integrating omics data into genome scale models in the example of an in silico model of Enterococcus faecalis using CoPE-FBA

Seyed Babak Loghmani[*] [1], Frank T.Bergmann[1], Brett G.Olivier[2], Nadine Veith[1], Ruth Großeholz[1], Tomas Fiedler[3], Ching Chiek Koh[4], Bernd Kreikemeyer[5], Ruedi Aebersold[4], Ursula Kummer[1]

[1]Bioquant, center for organismal studies (COS), Heidelberg University, Heidelberg, Germany, [2]Systems Bioinformatics, VU University Amsterdam, Amsterdam, Netherlands, [3]UMR/Institut für Medizinische Mikrobiologie, Virologie und Hygiene, Universitätsmedizin Rostock (UMR), Rostok, Germany, [4]Institute of Molecular Systems Biology, ETH Zurich, Zurich, Switzerland, [5]Institut für Medizinische Mikrobiologie, Virologie und Hygiene, Universitätsmedizin Rostock (UMR), Rostok, Germany

Secondary topic : Methodological developments for Systems Biology

Your abstract :

Genome-scale metabolic models (GSM) are stoichiometric representations of metabolic networks accounting for a large number of reactions in an organism. The calculation of fluxes in GSM is usually based on a steady-state assumption resulting in a net conversion rate of zero for each metabolite. Flux balance analysis is used to optimize flux distribution with respect to an objective function, e.g. biomass production. In general, there is no unique flux distribution that gives an optimal objective value, but rather solutions are contained in a solution space. CoPE-FBA is an analytical method for enumerating the number of solutions by defining several modules within the network[2]. These modules comprise reactions with variable flux values, resulting in a large number of solutions. Using this method, we investigated how a previously published method for integrating proteome data[2] reduces the solution space. We explored the effect of individual steps in this method on the number of solutions and compared results to find the extent to which these constrain the model in the example of an *in silico* model of *Enterococcus faecalis*. Not surprisingly, we can show that removing reactions based on experimental data strongly reduces solution space. However, adjusting reaction boundaries does not result in any substantial reduction with the only exception of exchange reactions which contribute indeed to the constraining of the solution space.

1. Kelk, S. M., Olivier, B. G., Stougie, L. & Bruggeman, F. J. Optimal flux spaces of genome-scale stoichiometric models are determined by a few subnetworks. *Sci. Rep.* **2,** 44–46 (2012)

2. Großeholz, R. *et al.* Integrating highly quantitative proteomics and genome-scale metabolic modeling to study pH adaptation in the human pathogen Enterococcus faecalis. *npj Syst. Biol. Appl.* **2,**16017 (2016)

Disclosure of Interest: None Declared

Improving multi-omics data integration via regression models using prior knowledge

Christoph.Ogris Ogris[* 1], Fabian Theis[1, 2], Nikola S. Müller[1]
[1]Institute of Computational Biology, Helmholtz Center Munich, Neuherberg, [2]Department of Mathematics, Technical University of Munich, Garching, Germany

Secondary topic : Methodological developments for Systems Biology

Your abstract : Over the past decade high throughput techniques made it possible to study biological mechanisms on a large scale and cost-effective manner. The resulting tremendous increase of omics data was not only the foundation for many public databases but also provided deep insights into complex biological processes. This clarified that biological systems are not controlled by single independently acting genes but are steered by an interplay of diverse biomolecules like proteins, genes or enzymes. Since these systems act across various omics information layers, many studies validate and strengthen their findings by measuring multiple omics levels.

Here, we present a regression based approach to integrate various omics levels and identify key features of the measured conditions. So far, most common analysis strategy is to explore all layers independently and search for common features afterwards. However, this assumes that all omics levels are contributing equally to the results and that there is no 'cross-omics' relationships within the data. In our approach we account for these issues by using all data points, from all omics levels, as independent variables for the regression model. Unfortunately, the large size of the feature space comes with two major drawbacks. On the on hand, the regression coefficients are unfeasibly small. On the other hand, the computational power explodes with the growing feature space. Therefore, we reduce the feature space using prior knowledge from public databases. For example, to identify the key features impacting the expression of a specific protein we only use those proteins, genes, mutations and DNA methylation sites, as covariates in the regression analysis, which have been previously associated to that protein. In a benchmark we evaluated the performance of four different penalized regression methods with and without prior knowledge. After selecting the best method we applied our approach to multi-omics TCGA data sets of eleven different tumor types, containing information of protein expression, mRNA expression, DNA methylation, mutation, copy number variation and clinical features. We were able to integrate the data and identify sets of cancer type specific features across all omic levels. These results demonstrate that our method successfully utilizes prior knowledge to boost the power of data integration and therefore vastly improves the interpretability of multi-omics studies.

Disclosure of Interest: None Declared

Multiscale Systems Biology - MULT

Beyond GRN-to-phenotype with circadian models, from genome sequence to ecology

Andrew Millar[* 1], Uriel Urquiza[2], Argyris Zardilis[1], Nacho Molina[1, 3]
[1]SynthSys and School of Biological Sciences, [2]UNIVERSITY OF EDINBURGH, Edinburgh, United Kingdom, [3]IGBMC, Strasbourg, France

Secondary topic : Modelling Networks and Circuits

Your abstract : The 24-hour circadian clock is a tractable biological process, where we may link our understanding of molecular regulation from the lab to the field (Millar, 2016, https://doi.org/10.1146/annurev-arplant-043014-115619). Breeders have selected alleles of clock-associated genes, suggesting its importance in multiple crops. To that end, we built mechanistic, mathematical models of the clock gene circuit and its outputs between germination and flowering (e.g. Seaton et al. MSB 2015 https://doi.org/10.15252/msb.20145766), and linked them in a Framework Model for Arabidopsis growth (Chew, Seaton et al. bioRxiv 2017; https://doi.org/10.1101/105437).

We recently moved beyond this GRN-to-phenotype approach. At small scales, Uriel Urquiza used absolute clock RNA and protein levels (copy numbers per cell) to replace the models' arbitrary units. Combining absolute RNA and protein data, biophysical data and TF-binding models (with Nacho Molina), we show how to use genome sequences as an input to predict timing function. Parameter fitting in these large models remains a critical step, where we adopted SloppyCell and we now work with Akman, Fieldsend et al. on new methods (see Akman abstract 9-292). At the ecological scale, Argyris Zardilis has linked a Framework Model refactored in the Chromar language (Honorato-Zimmer et al., ENTCS 2018 https://doi.org/10.1016/j.entcs.2018.03.008) up to the whole Arabidopsis lifecycle, across years and locations, to address ecological questions at the population scale. These are steps towards a 'crops in silico' approach, starting from increasingly-available crop genome sequences and reaching up to field traits. In future, such models might test the full causal chain of Genetics, from genome sequence via gene circuit and plant phenotypes, to fitness, selection of sequence variants and hence evolution of the genome sequence.

Funding: Conacyt (Mexico), EU TiMet project, BBSRC.
Acknowledgements: Dr. Robert Muetzelfeldt, Simulistics Ltd.; Prof. Gordon Plotkin, School of Informatics, U. of Edinburgh.

Disclosure of Interest: None Declared

Regulation of cellular heterogeneity by uneven molecular partitioning during the CD8 T-cell immune response

Simon Girel[* 1, 2], Jacqueline Marvel[3], Christophe Arpin[3], Olivier Gandrillon[1, 4], Fabien Crauste[1, 2]

[1]Dracula, Inria, [2]Institut Camille Jordan, CNRS, Villeurbanne, [3]CIRI, INSERM, [4]Laboratory of Biology and Modelling of the Cell, ENS Lyon, Lyon, France

Your abstract : The lymph-node resident naive CD8 T-cells are activated upon infection by an intra-cellular pathogen. Activated CD8 T-cells then mount an immune response, characterised by a program of cell proliferation, migration, differentiation and death. It is now well known that responding CD8 T-cells develop heterogeneous phenotypes, associated with heterogeneous intra-cellular molecular contents. Which mechanisms regulate that heterogeneity and how it impacts the immune response dynamics remain a matter of debate.

To address this question, we mathematically studied the contribution of uneven partitioning of molecular content at cell division to the regulation of molecular heterogeneity.

In a recent work [1], we designed an impulsive differential equation, where impulses are associated with cell division, to model the concentration of Tbet protein in a single dividing CD8 T-cell. High and low Tbet levels may be associated with two antagonistic cell fates: either cytotoxic effector or long-lived memory. Through the analysis of the impulsive equation, we studied the impact of uneven molecular partitioning on the emergence of effector and memory fates and discuss how variations in the degree of unevenness and in the cell cycle length affect the regulation and reversibility of the differentiation process.
In parallel, a hybrid discrete-continuous agent-based model of the early CD8 T-cell immune response has been developed in our team [2, 3]. It couples the discrete description of CD8 T-cell population dynamics with a continuous description of a molecular regulatory network, including Tbet protein. Based on our results from [1], we enriched this model to introduce an additional state of differentiation (memory) and employed it to evaluate the contribution of uneven molecular partitioning to the immune response dynamics.

[1] S. Girel and F. Crauste, Existence and stability of periodic solutions of an impulsive differential equation and application to CD8 T-cell differentiation, *J. Math. Biol.*, 2018.
[2] S. A. Prokopiou *et al.*, Multiscale Modeling of the Early CD8 T-Cell Immune Response in Lymph Nodes: An Integrative Study, *Computation*, 2014.
[3] X. Gao *et al.*, IL-2 sensitivity and exogenous IL-2 concentration gradient tune the productive contact duration of CD8+ T cell-APC: a multiscale modeling study, *BMC. Syst. Biol.*, 2016.

Disclosure of Interest: None Declared

New gnotobiotic mouse model to explore interactions between microbiome and host physiology in childhood stunting induced by chronic undernutrition

Marion Darnaud[* 1], Pascaline Bogeat[1], Hélène Dugua[1], Martin Schwarzer[2], François Leulier[3], Andrea Tamellini[1]

[1]Preclinical Models and Imaging Unit, BIOASTER, LYON, France, [2]Laboratory of Gnotobiology, Institute of Microbiology of the Czech Academy of Sciences, Nový Hrádek, Czech Republic, [3]Institut de Génomique Fonctionnelle de Lyon (IGFL), Université de Lyon, Ecole Normale Supérieure de Lyon, Centre National de la Recherche Scientifique, Université Claude Bernard Lyon 1, Unité Mixte de Recherche 5242, LYON, France

Your abstract : Childhood chronic undernutrition affects metabolism and hormonal signaling leading to stunting syndrome, which is associated with higher juvenile mortality rate and correlate with immune, cognitive and gut mucosal barrier deficits in adulthood.

Recent studies have highlighted the **role of gut microbiota on juvenile growth**. Germ-free mice colonized with undernourished child microbiota recapitulate the impaired growth phenotype. Besides, monocolonized mouse models have been used to demonstrate that specific bacterial strains can promote juvenile growth, interact with the somatotropic hormone axis and buffer the adverse effects of childhood chronic undernutrition. Moreover, another preclinical study has shown that gut microbiota, and possibly short-chain fatty acids produced by bacteria, restores bone mass, which is likely mediated by the insulin-like growth factor 1 (IGF-1). Taken together, these findings suggest that specific bacterial strains can reshape undernourished children microbiota and offer opportunities to improve juvenile growth and health.

Here we introduce a representative preclinical model of childhood stunting induced by chronic undernutrition in **gnotobiotic mice featuring a simplified and controlled murine microbiota, which recapitulates the phenotype observed with a complex murine microbiota**. We believe this new gnotobiotic mouse model is of interest to **explore the interactions between microbiome and host physiology, gain reproducibility, further decode the impact of gut microbiota and specific bacterial strains on juvenile growth, and develop novel microbiota-directed therapeutics.**

Disclosure of Interest: None Declared

Quantitative Systems Physiology - PHYS

How gene expression's response to cell physiological status determines gene order and its conservation in microbes.

Pablo Yubero[*1], Juan F. Poyatos[1]
[1]LOGIC OF GENOMIC SYSTEMS LAB (CNB-CSIC), Madrid, Spain

Your abstract : Gene expression control is one of the basic means by which bacteria adapt to changing environmental conditions. Apart from the specific action mediated by transcription factors (TFs), gene expression is also linked to the global physiological status of the cell. This underlies the global expression program, which is directly related to the availability of global resources like tRNA, free RNAP, proteome allocation and cell size. Since the pioneering work of the Copenhagen school of cell physiologists, it is known that cell's physiological state is determined by the growth rate independently of the exact composition of the growth medium.

Recently, the global expression program has gathered renewed attention since it introduces growth-rate dependencies in gene expression even in the case of constitutive "unregulated" genes. The growth-rate is thus found to take an active role in gene regulation by modifying the behavior of genetic circuits. In addition, the importance of the expression control exerted by TFs and the regulatory network has been questioned. While a few case studies examined the implications of this program, a genome-wide assessment of its effect is still lacking.

Here, we present a model to quantify growth-rate dependencies of the chromosomal promoter activities of over 1800 genes of *Escherichia coli* with fluorescent transcriptional reporter plasmid data. In particular, we find that constitutive genes show a variety of responses to an increase in growth rate, and that they are not equally affected by global regulation. Notably, and independently of their response, promoters sensitive to growth rate are closer to the origin of replication of the chromosome. We thus postulate that both global regulation and the habitat of the bacteria acts as a driving force of genomic architecture. This is confirmed by examining the relation between position conservation of *E. coli* genes in 100 bacterial species and the environmental variability of the species' habitat.

Disclosure of Interest: None Declared

A growth-mediated negative feedback loop lowers the sensitivity to antibiotics

S. Andreas Angermayr[*1], Guillaume Chevereau[2], Tobias Bollenbach[1]
[1]University of Cologne, Cologne, Germany, [2]INSA Strasbourg, Strasbourg, France

Your abstract : Understanding how pathogens respond to antibiotics is relevant for establishing effective disease treatments and for fighting drug resistance evolution. The environment affects the growth of bacteria and their susceptibility to antibiotics. Using a set of six different antibiotics—representing the main modes of action—we tested how growth rate influences their efficacy. For trimethoprim—an antibiotic used widely to treat urinary tract infections—we have found a reduction of susceptibility for slow growing *Escherichia coli* cultures. The folate-synthesis inhibitor trimethoprim shows a consistently observed very shallow dose-response curve. Using four different means of growth limitation—each encompassing a broad range of growth rates—we can change the steepness of the dose-response curve for trimethoprim. Combining these results, we have established a general growth-mediated negative feedback loop that controls the dose-sensitivity for trimethoprim. Next, we asked for the molecular mechanism governing antibiotic susceptibility and dose-sensitivity. Lowered growth rate leads to an increased drug target-expression level which in turn lowers the dose-sensitivity to the drug. The growth-mediated negative feedback offers an explanation for the shallow dose-response curve for trimethoprim. These results have implications for antibiotic efficacy in clearing infections and for resistance evolution. Negative growth-mediated feedback offers an opportunity for slowing the evolution of drug resistance.

Disclosure of Interest: None Declared

Single cell membrane potential dynamics under stress in bacteria

Dong-Yeon Lee[* 1], Leticia Galera-Laporta[2], Maja Bialecka-Fornal[1], Eun Chae Moon[1], Jordi Garcia-Ojalvo[2], Gurol Suel[1]

[1]Division of biological sciences, University of California, San Diego, La Jolla, United States, [2]Universitat Pompeu Fabra, Barcelona, Spain

Your abstract : The membrane potential is a fundamental property of any cell. However, only limited data exist on bacterial membrane dynamics due to their small size. Here we measured the membrane potential dynamics in individual bacteria under stress such as mild antibiotic challenges. Specifically, we used a microfluidic device and time-lapse fluorescent microscopy to determine the dynamics of growth and membrane potential at the single-cell level. Unexpectedly, we find that bacteria transiently hyperpolarized as a response to stress. The results indicate that the interplay between cellular stress and membrane potential dynamics is not restricted to a class of antibiotics, but rather constitutes a general stress response that could provide new insights in bacterial physiology and consequently bacterial control.

Disclosure of Interest: None Declared

Mathematical modelling of cell cycle: past and future

Rahuman Sheriff[* 1], Matthieu Maire[1], Vijayalakshmi Chelliah[1], Nicolas Le Novere[2], Henning Hermjakob[1]

[1]BioModels, EUROPEAN BIOINFORMATICS INSTITUTE (EMBL-EBI), [2]Babraham Institute, Cambridge, United Kingdom

Secondary topic : Modelling Networks and Circuits

Your abstract : Cell cycle is one of the most important cellular processes that include coordination of cell-growth, DNA replication and cell division in a proliferating cell. This process has been quantitatively studied using several 'clock + checkpoint' models (Tyson and Novak, Curr Biology 2008) that can explain the key aspects of cell cycle regulation. Dysregulation of cell cycle pathways can result in the formation of cancer or apoptosis. Quantitative models are increasingly used to study cell regulations. Several cell cycle models can be found in the literature from last five decades, from the 1960s (Koch and Schaechter, J Gen Microbiol 1962) until recent times (Barr et al. 2017, Nature comm, Heldt 2018, bioRxiv). To make these models easily sharable and readily available to the broader scientific community, we performed a targeted curation of published cell cycle models pertaining to various cell cycle phases (G1, S, G2 and M) and Checkpoints. Currently, over 100 kinetic models are curated, including numerical simulation and enrichment with the cross-reference to other data resources and ontologies. These curated models are disseminated through BioModels portal in a ready-to-use SBML format that can be directly imported into various modelling and simulations software such as COPASI, CellDesigner, MATLAB Simbiology toolbox, etc. Thereby our resource will facilitate model reproducibility, re-use and repurposing. We further systematically analysed the cell cycle models landscape and discoursed the contributions of these models to the field, highlighting the areas where more focused research is required.

Disclosure of Interest: None Declared

Vesicular trafficking dynamics enable context-dependent regulation of ErbB receptor activity and signaling

Yannick Brüggemann[*1], Philippe Bastiaens[1]
[1]Max Planck Institute of Molecular Physiology, Dortmund, Germany

Secondary topic : Single-cell Systems Biology

Your abstract : The extracellular regulated kinases Erk1 and Erk2 comprise a subfamily of the mitogen-activated protein kinases (MAPK), which respond to a broad range of external and internal stimuli and mediate numerous cellular responses. While the temporal regulation of Erk activity has been extensively studied, the spatial organization and function of Erk activity is still poorly understood. We examined how ligand-specific ErbB receptor trafficking determines Erk signaling dynamics and localization. We found that EGF or heregulin (HRG) differentially modulate ErbB receptor trafficking to generate distinct spatiotemporal patterns of receptor activities, leading to the activation of Erk from different subcellular compartments (plasma membrane and endosomes). The subcellular localization of Erk activation influences its interaction with different effector proteins and thereby generates ligand-specific cellular responses. Proliferative Erk signals are transmitted to the nucleus, irrespective of their spatial origin, while the Erk dependent phosphorylation of pro-migratory effectors relies on membrane proximal Erk activity.

Disclosure of Interest: None Declared

The multiplex phase interlocker – a novel and robust molecular design synchronizing transcriptional with cell cycle oscillators

Thierry Mondeel[1], Christian Linke[1], Silvia Tognetti[2], Oleksandr Ivanov[3], Wolfram Liebermeister[4], Mart Loog[5], Hans Westerhoff[1, 6], Francesc Posas[2], Matteo Barberis[* 1, 6]
[1]Synthetic Systems Biology and Nuclear Organization, University of Amsterdam, Amsterdam, Netherlands, [2]Departament de Ciències Experimentals i de la Salut, Universitat Pompeu Fabra, Barcelona, Spain, [3]Theoretical Research in Evolutionary Life Sciences, University of Groningen, Groningen, Netherlands, [4]Institut für Biochemie, Charité - Universitätsmedizin Berlin, Berlin, Germany, [5]Institute of Technology, University of Tartu, Tartu, Estonia, [6]Molecular Cell Physiology, VU University Amsterdam, Amsterdam, Netherlands

Secondary topic : Modelling Networks and Circuits

Your abstract : Time-dependent responses of biological networks are associated with oscillatory behavior of their components at a proper frequency. The eukaryotic cell cycle is an example of a such robustly designed network, with a transcriptional oscillator being interlocked with waves of cyclin-dependent kinases (cyclin/Cdk) to guarantee its frequency. Therefore, molecular designs that exhibit a proper frequency of cyclin/Cdk oscillations are inherently crucial for a timely cell cycle progression. Although details about transcription of cyclins, the regulatory subunits of Cdk, are available, a lack of understanding exists about network motifs responsible for the precise timing and frequency of cyclin/Cdk oscillations.
We have recently identified in budding yeast a transcriptional cascade that regulates the relative timing of waves of mitotic (Clb) cyclin expression, which involves the Forkhead (Fkh) transcription factors (TF) that re conserved among eukaryotes. Here we investigate the robustness of molecular designs responsible for timely cyclin/Cdk oscillations, with the aim to unravel the network motif(s) that interlock Clb waves through Fkh-mediated signaling.
An integrated computational and experimental framework is presented. A kinetic model of the cyclin/Cdk network is fitted to *in vivo* quantitative data of Clb dynamics. Robustness analyses are then performed by testing 1024 possible network motifs for their ability (i) to fit Clb oscillations and (ii) to generate sustained oscillations in the form of limit cycles, on which sensitivity analysis is conducted. A novel regulatory motif, coined as *Multiplex Phase Interlocker* (MPI), is unravelled, with a linear, Fkh-mediated cascade among Clb cyclins [Clb5 (S phase) → Clb3 (G2 phase) → Clb2 (M phase)] being pivotal for a timely synchronization of Clb/Cdk1 oscillations. This motif uniquely describes a molecular timer (TF) that relies on separate inputs (Clb/Cdk1) converging on a common target (TF itself). Within the motif, a progressive Fkh activation may be realized by Clb/Cdk-mediated phosphorylation, as suggested by our quantitative data. Furthermore, a Clb3/Cdk1-mediated positive feedback loop is identified as a dominant network motif responsible for sustained Clb/Cdk1 oscillations. Altogether, our integrative approach pinpoints how robustness of the cell cycle control is realized by revealing a novel and conserved principle of design that ensures a timely interlock of transcriptional and cyclin/Cdk oscillations.

Disclosure of Interest: None Declared

Membrane potential as an indicator of the cellular state

Leticia Galera-Laporta*[*1], Dong-Yeon Lee*[2], Maja Bialecka-Fornal[2], Eun Chae Moon[2], Jordi Garcia-Ojalvo[1], Gurol Suel[2]

[1]Experimental and Health Sciences, Universitat Pompeu Fabra, Barcelona, Spain, [2]Division of biological sciences, University of California, San Diego, La Jolla, United States

Secondary topic : Quantitative Systems Physiology

Your abstract : Membrane potential is a fundamental property of any living cell. In bacteria, membrane potential is implicated in several mechanisms, such as nutrient uptake, energy production and cell motility. In spite of the importance of this cellular property, very little is known about its variability and dynamics at the single-cell level. By using a membrane potential reporter, Thioflavin-T (ThT), we captured the dynamics of hundreds of cells by time-lapse fluorescence microscopy. We observed that a small percentage of the population presents a characteristic transient hyperpolarization that could be linked to cellular stress. To test this hypothesis, we performed chemical and genetic perturbations in order to alter the cellular state. Interestingly, we observed that under different kind of stresses, there is an increase in the hyperpolarized cell fraction. This dynamic change in the bacterial membrane potential could be due to the efflux of positive ions. These findings could suggest membrane potential as a reporter of the cellular state.

Disclosure of Interest: None Declared

Single-cell Systems Biology - CEL

Inferring hidden states of cells from direct lineage tracking data

Tetsuya Kobayashi[*1], Yuki Sughiyama[1], So Nakashima[1]
[1]INSTITUTE OF INDUSTRIAL SCIENCE, THE UNIVERSITY OF TOKYO, Tokyo, Japan

Secondary topic : Quantitative Systems Physiology

Your abstract : Heterogeneity in a population of cells is a strategy of the cells to survive in an unpredictable environment. Persistence of bacteria is a typical example of how bacteria exploit their heterogeneity to circumvent the risk of extinction under antibiotic treatment.
Recent advancements in cell tracking technologies enable us to observe growing cells over a hundred generations, which reveal that the persistence is a more complicated phenomenon than just the existence of dormant cells and suggests that the proliferative activities are somehow linked to the extent of resistance to the antibiotics.
Nonetheless, we are lacking appropriate methods to infer the heterogeneity of the proliferative activities of cells from direct observations of growing cells.
In this work, we present an Expectation-Maximization (EM) based algorithm to infer the hidden states of cells from tracking data of cells. Because of divisions of the cells, we cannot naively apply the original EM algorithm to the data, and so we modified the EM algorithm to account for the tree structure of the tracked cells and related over-representation of the quickly growing cells in the lineage tree.
By applying our method to a long-term lineage data of E.coli, we identified hidden states of the cells that may be linked to the slowing changing activity of the cells.
This method may contribute to facilitate and deepen our understanding of the resistance of pathogens and cancer cells to different kinds of drugs.

Disclosure of Interest: None Declared

Kinesin-5 contributes to spindle-length scaling in the evolution of cancer toward metastasis

Hsiao-Chun Huang* [1]
[1]NATIONAL TAIWAN UNIVERSITY, Taipei, Taiwan

Secondary topic : Systems Medicine

Your abstract : During natural evolution, the spindles often scale with cell sizes to orchestrate accurate chromosome segregation. Whether in cancer evolution, when the constraints on genome integrity are relaxed, cancer cells may evolve the spindle to confer other advantages has not been investigated. Experimentally, using invasion as a selective pressure *in vitro*, we found that a highly metastatic cancer clone displays a lengthened metaphase spindle, with faster spindle elongation that correlates with transiently elevated speed of cell migration. We found that the sliding motor kinesin-5 is upregulated in this malignant clone, and weak inhibition of kinesin-5 activity could revert the spindle to a smaller aspect ratio, decrease the speed of spindle pole separation, and suppress post-mitotic cell migration. Computationally, we constructed a force-balance model that describes pole-pole spacing as a balance of antagonistic forces exerted on the poles by sliding motor proteins and microtubule-depolymerizing enzymes. The model suggested that higher speed of spindle elongation arose from a higher outward force exerted by up-regulation of Kinesin-5. To confirm model's prediction, we plan to use imaging-based matrix deformation assay to test the hypothesis that in the metastatic clone, faster spindle elongation is associated with higher extracellular protrusive force, which leads to higher capacity to overcome mechanical constrains and disseminate. This study implicates that lengthened spindles could potentially serve as a cellular biomarker for metastatic cancer clones in the clinic.

Disclosure of Interest: None Declared

Predicting the future direction of cell movement with convolutional neural networks

Shori Nishimoto[*1], Yuta Tokuoka[1], Noriko Hiroi[2], Akira Funahashi[3]
[1]Graduate School of Science and Technology, Keio University, Yokohama, [2]Faculty of Pharmaceutical Sciences, Sanyo-onoda City University, Yamaguchi, [3]Department of Biosciences and Informatics, Keio University, Yokohama, Japan

Your abstract : Image-based deep learning, such as Convolutional neural networks (CNNs), has recently been applied to the bioimage analysis, producing impressive results, especially in the cell classification. These application cases of CNNs remain at the classification of current cell state from the image. However, recent studies demonstrate that current and/or past cell shape, which dynamically changes, influences the future cell fate. An interesting question is whether CNNs could predict the future cell fate based on current and/or past cell shape.
Here, we focused on dynamic cell movement where current and/or past cell shape can influence the future cell fate. Our hypothesis was that CNNs could learn such cell shape and predict the future direction of cell movement from a single image patch of a cell at a certain time.
We prepared image datasets from time-lapse phase-contrast microscopic images of cell movement of NIH/3T3 cells and U373 cells, respectively. Using these datasets, we trained and validated CNN models to predict the future direction of cell movement from a single image patch of a cell at a certain time. CNN models achieved Mean Classification Accuracy (MCA) of 85.8% for NIH/3T3 cells, 85.4% for U373 cells.
Furthermore, to reveal how and why CNN models could predict the future direction, we visualized the features on the cell images that were learned by CNN models and contributed to their prediction. As a result, we identified the morphological features, such as the protrusions, the trailing edge, and the polarity of cell shape, which are reported to determine the direction of cell movement.
Our results indicated that CNNs have the potential to predict the future cell fate from current and/or past cell shape. Results of visualization also indicated that the morphological features influential in the future cell fate could be identified in a top-down manner with CNNs.

Disclosure of Interest: None Declared

Analysis of the effects of inhibitor drugs against ribosome biogenesis by using self-organized maps

Muge Kasim* [1], Elif Gencturk[1], Kutlu Ulgen [1]
[1]Chemical Engineering, BOGAZICI UNIVERSITY, İstanbul, Turkey

Your abstract :

ANALYSIS OF THE EFFECTS OF INHIBITOR DRUGS AGAINST RIBOSOME BIOGENESIS BY USING SELF-ORGANIZED MAPS

Müge Kasım*, Elif Gençtürk*, Kutlu Ö. Ülgen*
*Department of Chemical Engineering, Biosystems Engineering Lab. Bebek/İstanbul, 34342
muge.kasim@boun.edu.tr

Abstract: SOM is a method of mapping the multidimensional data to the lower dimensions (one or two) protecting the original information. SOM is used to visualize the sample and group centered data, gene set enrichment analysis and similarity analysis between samples. Researchers can interpret the multidimensional data more effectively, with a little computing time and easy to read maps by using SOM analysis. In the literature, it is reported that the overexpression of genes that are responsible of ribosome biogenesis may cause the cancer. By using that knowledge, in this study, SOM analysis was used to investigate the ribosome biogenesis such as which genes were suppressed or overexpressed under various inhibitor drugs. Data of the response of the *S. cerevisiae* yeast strains against hydroxyurea and rapamycin treatment were used to perform SOM analysis and the changes in the gene expression levels were investigated. The expression level of NOP56 gene, which is thought to take part in ribosome biogenesis, was seen to be decreased when the hydroxyurea and rapamycin treatments were applied. The results were compared with the experimental studies, which were based on one and two phase microfluidic systems on chip. The ultimate goal of this study is to suggest a treatment strategy to diseases like ataxia and cancer, by using the model organism of eukaryote cells, the yeast cells.

Disclosure of Interest: None Declared

Polygenic standing variation can turn a homogeneous environmental response into a binary, highly stochastic one

Magali Richard[1], Claire Burny[1], Florent Chuffart[1], Helene Duplus-Bottin[1], Etienne Fulcrand[1], Marianne Entrevan[1], Gael Yvert[*1]
[1]Laboratory of Biology and Modeling of the Cell, CNRS, ECOLE NORMALE SUPERIEURE DE LYON, Lyon, France

Secondary topic : Evolutionary and Ecological Systems Biology

Your abstract : Populations of cells subjected to environmental stimulations may respond gradually (all cells adapting together) or as a mosaic (some cells adapting early and others later). These two types of response can have different consequences: in the latter case, subtypes of adapted and non-adapted cells are generated and co-exist, which may constitute a basis for differentiation, tissue patterning or randomization. Here we investigated whether and how natural genetic variation can change one type of response into the other. Using the yeast *Saccharomyces cerevisiae* galactose pathway as an experimental model system, we interrogated response dynamics differences between natural strains from the wild and we mapped the underlying genetics. We found that control of the dynamic properties (gradual or mosaic) is highly polygenic and is largely driven by loci that were not previously associated with the well-known GAL regulatory network. Our observations illustrate how stochasticity of gene activation can emerge from polygenic combinations of natural alleles.

Disclosure of Interest: None Declared

Single-cell dynamics of cytokine-secreting immune cells

Yacine Bounab[1], Sophie Dixneuf[2], Trang Tran[3], Maxime Mistretta[1], Fabienne Venet[4, 5], Iain Gillespie[6], Pierre Cortez[7], Virginie Moucadel[8], Philippe Leissner[9], Julien Textoris[8, 10, 11], Andrew Griffiths[12], Cyril Guyard[9], Christophe Vedrine[* 1] and REALISM study group

[1]Biological microsystems and advanced optics engineering unit, BIOASTER, PARIS, [2]Biological microsystems and advanced optics engineering unit, BIOASTER, LYON, [3]Genomics and Transcriptomics Technology Unit, BIOASTER, PARIS, [4]EA7426 "Pathophysiology of Injury-induced immunosuppression", Université Claude Bernard Lyon 1- Hospices Civils de Lyon - bioMérieux, [5] Immunology Laboratory, Hospices Civils de Lyon - Université Claude Bernard Lyon 1, LYON, France, [6]GlaxoSmithKline, Brentford, United Kingdom, [7]Sanofi Aventis, Chilly-Mazarin, [8]Medical Diagnostic Discovery Department (MD3), bioMérieux, Marcy-l'Étoile, [9]BIOASTER, [10]EA7426 "Pathophysiology of Injury-induced immunosuppression", Hospices Civils de Lyon - bioMérieux, [11]Anesthesiology and Critical Care Medicine, Hospices Civils de Lyon - Université Claude Bernard Lyon 1, LYON, [12]ESPCI Paris, PSL Research University, PARIS, France

Your abstract : Dynamic characterization of immune responses at the single cell level is hampered by technological limitations. We have developed a simple and robust microfluidic platform to confine in 50-pL droplets a single primary human monocyte, fluorescent probes for caspase and mitochondrial activities, and a sensitive magnetic nanobeads binding assay in order to assess cytokine secretion, endocytosis and cell viability over time. A droplet monolayer was incubated in a glass chamber and analyzed by real-time fluorescence microscopy and automate software for image processing. Monocytes remained viable within the droplet for over 10 hours and secreted Tumor Necrosis Factor–a (TNF-a) was detected only 30 min following stimulation by lipopolysaccharide (LPS). We identified distinct dynamic secretion profiles from over 3000 single human monocytes in a single experiment. Our platform offers a new improved research tool for mapping cellular heterogeneity responses and secretion dynamics for different cell types. Significant technical advances in nanobeads functionalization, microfluidic chamber fabrication, and a customized image-processing algorithm improve the sensitivity and robustness of the assay.

Disclosure of Interest: None Declared

What makes a cell plastic?

Mirko Francesconi[*1], Bruno Di Stefano[2], Ben Lehner[1], Thomas Graf[3]
[1]Systems Biology, CRG, Barcelona, Spain, [2]Harvard University, Cambridge, United States, [3]GENE REGULATION, STEM CELLS AND CANCER, CRG, Barcelona, Spain

Secondary topic : Developmental Systems Biology

Your abstract : Some somatic cells are plastic: they can be converted into other specialized cell types (transdifferentiation) or into iPS cells (reprogramming) when transcription factors are over-expressed. A detailed description of these cell fate conversion processes is still lacking. For example, do cells convert fates as homogenous populations or through a diversity of paths? Do all cells convert with the same speed? And what are the determinants of variation in the speed and path of cell fate conversion? More fundamentally, if an individual cell is more susceptible for conversion into one fate, is it also more susceptible to conversion into alternative fates? For example, are cells more susceptible to reprogramming into iPS cells also more susceptible to trans-differentiation into another specialized cell type? To address these questions, we monitored the highly efficient C/EBPa-mediated conversion of pre-B cells into macrophages and iPSCs at single cell level by single-cell RNAseq. We show that even in these two highly efficient systems, cells differ in both their conversion speed and path. Differences in Myc activity and cell size in the starting population predict this heterogeneity in a reciprocal manner: Myc^{high} large pre-BII cells transdifferentiate slowly but reprogram efficiently, while Myc^{low} small pre-BII cells transdifferentiate rapidly but fail to reprogram. Strikingly, differences in Myc activity also predict reprogramming efficiency across a wide range of somatic cell types. Thus, we show that the rate and path of cell fate conversions depends on the starting cell state and that a somatic cell's propensity for either transdifferentiation or reprogramming can be uncoupled.

Disclosure of Interest: None Declared

Scalable visualization and exploration of single-cell omics data

Marcin Tabaka[*1]
[1]Regev Lab, Broad Institute, Cambridge, United States

Secondary topic : Methodological developments for Systems Biology

Your abstract : The recent progress in the development of high-throughput single-cell methods allows researchers to study cell types and states of millions of cells. Thus, there is a great need for memory efficient and fast tools for visualization and exploratory analysis of massive single-cell datasets. We developed a lightweight R package for interactive visualization and exploration of single-cell omics data that scales up to a billion cells. It provides a solution to common tasks in the single-cell data exploration and supports an efficient retrieval of cell features from massive expression matrices stored on a disk from compressed text or HDF5 file formats. We will show the functionality of the package on the large-scale scRNA-Seq datasets from human bone marrow and reprogramming of mouse embryonic fibroblasts to induced pluripotent stem cells along the 18-day time course of iPSC induction. Moreover, I will describe biological insights that emerged from the analysis of these single-cell datasets.

Disclosure of Interest: None Declared

Dynamic signal integration drives an anticipatory response in Saccharomyces cerevisiae glucose transport

Luis Montano[*1], Iseabail Farquhar[1], Peter Swain[1] and Swain Lab
[1]SynthSys, UNIVERSITY OF EDINBURGH, Edinburgh, United Kingdom

Secondary topic : Modelling Networks and Circuits

Your abstract : Organisms must constantly face and adapt to environmental change. Although unpredictable events may inevitably impose threats, temporally correlated changes may also provide opportunities from which organisms can profit. Indeed, for nutrient transport, it is not clear how organisms distinguish the threats such as looming depletion, from the opportunities, such as a low but rising concentration of nutrients. Deciphering an environment's dynamic identity (its change rate or frequency) could be a highly valuable asset for a cell to elicit an accurate physiological response.

When nutrients appear, The budding yeast must generally decide to invest in either low affinity and high affinity transport. As fluctuations in nutrient levels can quickly render any transporter's capabilities obsolete, the payoff of producing a transporter may be larger if produced when its need is imminent. Here, we wondered whether the kinetics of extracellular glucose helps to establish priority in glucose transport. Transport affinity is tightly linked with the switch between glucose fermentation and respiration in cancer cells and industrial bioprocesses.

We show that the yeast glucose sensing network uses dynamic glucose cues to orchestrate activation of glucose transportersHXT1-HXT7. In particular, intermediate affinity HXT4 activates exclusively during a glucose downshift, in contrast with other transporters. We explore how pathway mutants alter HXT4 dynamics, which together with modelling modeling offer deep mechanistic insight on how the network achieves encoding of complex environmental history. Furthermore, we model and analyse the key role of the pulsatile dynamics of major glucose repressor Mig1 during a glucose upshift to establish transport priority.

Altogether these results show how a complex network can process a single input to conditionally repress and derepress a promoter at the same glucose level depending on history, and suggests that glucose transport could contribute to fitness in transient environments by yet unexplored mechanisms.

Disclosure of Interest: None Declared

Systems Medicine - MED

Perturbation biology links temporal protein changes to drug responses in a melanoma cell line

Elin Nyman[*1], Richard Stein[2], Chris Sander[2]
[1]LINKÖPING UNIVERSITY, Linköping, Sweden, [2]Dana-Farber Cancer Institute, Boston, United States

Secondary topic : Modelling Networks and Circuits

Your abstract : Many melanoma tumors initially respond to targeted drugs. Such targeted drugs are developed to attack growth signaling pathways which are increased from mutations in the tumor cells. However, the response to targeted drugs in melanoma is often temporary due to short-term adaption and long-term resistance development. To get closer to understand these mechanisms, we study in detail the short-term adaptation of cancer cells to a set of targeted drugs alone and in combination. Specifically, we systematically measure the time-resolved response of 124 key proteins to 54 targeted drug combinations in a window of 72 hours in the A2058 melanoma cell line, which carries a common mutation (V600E) in the gene BRAF. Furthermore, the cell line is resistant to targeted drugs that are used in the clinic, and therefore a good model to study drug resistance. We also measure cell growth and apoptosis as readouts for drug efficacy. This rich and unique dataset enables us to build ordinary differential equations based network models that capture not only the temporal patterns of the measured proteins, but also allows to predict the effect of unseen drug combinations. Based on the network models, we propose novel perturbations that are predicted to overcome the short-term adaption by targeting combinations of the proteins STAT5a, EGFR, and IRS1. Despite our focus on overcoming short-term adaptation, the insight from our data-derived modeling efforts may also hold for understanding the mechanism of long-term acquired resistance and may contribute to identify drug targets that overcome drug resistance in melanoma patients.

Disclosure of Interest: None Declared

Analysis of brain transcriptomes reveals candidate genes and pathways influenced by cerebrovascular diseases

Cho-Yi Chen[*1]
[1]NATIONAL YANG-MING UNIVERSITY, Taipei, Taiwan

Secondary topic : Modelling Networks and Circuits

Your abstract : Cerebrovascular diseases (CeVD) are a group of medical conditions that impair circulation of blood to the brain, including stroke, transient ischemic attack (TIA), embolism, aneurysm, and other circulatory disorders affecting the brain. Here, we investigated the effects of having CeVD history on the molecular signature of brain regions by comparing gene expression profiles from several brain tissues between cohorts with and without CeVD history. We first clustered brain tissue samples from GTEx RNA-Seq dataset into three clusters based on the overall gene expression similarity. Then we performed differential expression (DE) analyses for each cluster using a linear mixed model that controls covariates and the individual random effect. Cross-region DE genes were ranked by the combined q-values derived from the mixed model using Fisher's method. Functional enrichment analyses were performed using Gene Set Enrichment Analysis (GSEA) program. We identified hundreds of DE genes and many of them are related to endothelial or brain functions and associated diseases. We found that *STAB1* was highly overexpressed across brain regions in the CeVD cohort, and the upregulation of *STAB1* in brain tissues may contribute to weaker self-defense mechanisms against lesions in the brain. To better understand the drivers of these differences, we used network modeling technique to infer sample-specific gene regulatory networks, which enabled us to identify potential dysregulation in the upstream network paths of those CeVD candidate genes. Our results suggest a list of candidate genes and pathways that may be dysregulated in the brains of people with CeVD history, implying that suffering from CeVD could pose potential hazard to the brain.

Disclosure of Interest: None Declared

A pan-cancer analysis of differential protein interactome

Gizem Gulfidan[*1], Beste Turanli[1,2], Kazim Yalcin Arga[1]
[1]Department of Bioengineering, Marmara University, [2]Department of Bioengineering, Istanbul Medeniyet University, Istanbul, Turkey

Secondary topic : Multi-omics

Your abstract : Cancer is one of the most common causes of death all over the world. Therefore, it is crucial to understand the molecular mechanisms underlying cancer for development of effective diagnosis, prognosis, and treatment strategies. In order to reach a systems-level understanding of a phenotype, it is mandatory to decipher all functional interactions among proteins. The studies which have started with the comprehensive examination of alterations in cancer genes currently continue trying to understand the role of protein-protein interactions (PPIs) in tumorigenesis. To get a better understanding of the molecular mechanisms that discriminate specific cancer from others, in our study, we comparatively analyzed the changes in the interaction patterns of proteins, and thus obtained a differential view of human protein interactome among 32 major cancer types. For this purpose, we considered the transcriptome and clinical data (>10 000 individuals) from The Cancer Genome Atlas (TCGA) describing both inter-individual and inter-tumor variation patterns. Using gene expression levels as a proxy, we identified PPIs with minimum uncertainty in each cancer type. This “differential interactome” approach led to the identification of PPIs that are activated or repressed in each cancer relative to the others. The results showed that a certain fraction of proteins is differentially interacted in cancers and has an impact on overall patient survival. The analysis provided the characterization of differentially interacting proteins (DIPs) representing significant changes in their interaction patterns during tumorigenesis. The analyses of similarity among different cancers based on differential PPI profiles pointed out that no general protein interactome profile applied to all cancers. On the other hand, it seems to be possible to generate cancer-specific PPI subnetworks, which might be useful in understanding tumorigenesis and improvement of treatment strategies.

This study was supported by Marmara University Scientific Research Projects Committee (BAPKO) in the context of the project FEN-C-YLP-170118-0013, and The Scientific and Technological Research Council of Turkey (TUBITAK) through the project 116M014.

Disclosure of Interest: None Declared

A stepwise integrative analysis pipeline for exploring host-microbiota interaction and symptom association

Annikka Polster[*1], Lena Öhman[2], Julien Tap[3], Muriel Derrien[3], Boris Le Neve[3], Johanna Sundin[2], Hans Törnblom[4], Marija Cvijovic[5], Magnus Simren[4]
[1]Internal Medicine and Clinical Nutrition, Gothenburg University, Göteborg, [2]Microbiology and Immunology, Gothenburg University, Gothenburg, Sweden, [3]Danone Nutricia, Palaiseau, France, [4]Internal Medicine and Clinical Nutrition, Gothenburg University, [5]Mathematical Sciences, Gothenburg University and Chalmers University, Gothenburg, Sweden

Secondary topic : Multi-omics

Your abstract : A growing body of evidence confirms the important role of gut microbiota in health and disease, but the detailed mechanisms of interaction between gut microbiota and host are unknown. Given the difficulties in experimentally studying these interactions both *in vivo* and *in vitro*, computational approaches useful for determining which microbial species interact with which host factors may greatly enhance our understanding of this interaction and identify which mechanisms are most promising targets for detailed experimental studies. We have developed a stepwise analysis pipeline, in which rank correlations between microbial species and host factors are utilized as a proxy for estimating the grade of interaction between the respective variables, and plotted as network graphs to facilitate the intuitive interpretation of these interactions. The relevance of the respective interaction in the pathophysiology of diseases is estimated by both statistical testing and comparisons between healthy and diseased individuals, as well as by creating a multiplex network graph associating network motifs to key symptoms.
We have tested the applicability of this pipeline in a pilot study on humans, utilizing data from healthy individuals (HC) as well as patients with Irritable Bowel Syndrome (IBS), a gastrointestinal disorder characterized by various chronic symptoms and incompletely understood pathophysiology.
In this pilot study, network motifs, indicating close associations of the respective variables, were identified in both groups. A comparison between HC and IBS showed distinct differences in network structure, indicating differences in host-microbiota interaction between these two groups. Network motifs which were present in IBS but not in HC were additionally linked to key symptoms, supporting the relevance of these variables for understanding IBS pathophysiology. This pilot study therefore confirmed our stepwise integrative analysis pipeline as a useful approach for improving our understanding of host-microbiota interaction in health and disease.

Disclosure of Interest: A. Polster: None Declared, L. Öhman: None Declared, J. Tap Conflict with: Employee of Danone Nutricia, M. Derrien Conflict with: Employee of Danone Nutricia, B. Le Neve Conflict with: Employee of Danone Nutricia, J. Sundin: None Declared, H. Törnblom Conflict with: served as Consultant/Advisory Board member for Almirall, Danone, and Shire, M. Cvijovic: None Declared, M. Simren Conflict with: received unrestricted research grants from Danone, and Ferring Pharmaceuticals, and served as a Consultant/Advisory Board member for AstraZeneca, Danone, Nestlé, Almirall, Allergan, Albireo, Glycom, and Shire, and as a speaker for Tillotts, Menarini, Takeda, Shire, Allergan, and Almirall.

Global analysis of protein and mRNA expression levels in medulloblastoma reveals distinct activated pathways between tumor subgroups

Loredana Martignetti[* 1], Antoine Forget[2], Laurence Calzone[1], Arnau Montagud[1], Stéphane Liva[3], Alexandre Sta[1], Florent Dingli[4], Guillaume Arras[4], Jaime Rivera[4], Damarys Loew[4], Patrick Poullet[1], Emmanuel Barillot[1], Olivier Ayrault[2]
[1]INSTITUT CURIE / INSERM U900 / PSL Research University / Mines Paris Tech, [2]INSTITUT CURIE / CNRS UMR 3347, INSERM U1021 / PSL Research University, [3]Institut Curie / PSL Research University, [4]INSTITUT CURIE / Proteomics and Mass Spectrometry Laboratory / PSL Research University, Paris, France

Secondary topic : Multi-omics

Your abstract : In modern oncology, cell-molecular heterogeneity of human tumors is believed to be a major cause of drug resistance and subsequent disease recurrence. Therefore, the goal of precision medicine is to dissect complex molecular profile of each patient's tumor to understand mechanisms underlying disease aggressiveness and drug resistance. In this study, an integrative analysis was carried out including transcriptomic profiling as well as cutting-edge deep proteomics and phosphoproteomics measurements of medulloblastoma (MB) patients, the most common malignant brain tumor of childhood, to decipher signaling pathways and molecular mechanisms underlying different tumor subgroups. Proteomic characterization led to the discovery of unappreciated signalling pathways specific to poor outcome subgroups (G3 and G4), not previously apparent in transcriptomic comparisons. Importantly, specifically in G3 and G4, mRNA expression poorly correlated with protein expression. This discrepancy has a subgroup specific pattern suggesting a hallmark role of post-transcriptional regulatory mechanisms in driving cancer subtypes. We therefore focused on significant discrepancies between mRNA-protein levels to investigate possible mechanisms of protein abundance regulation acting after the setting of mRNA levels, including translational and degradative mechanisms. Overall, our data highlight a complex control of protein/mRNA balance in medulloblastoma tumor subgroups, providing compelling evidence that post-transcriptional regulation is highly subgroup-dependent.

Disclosure of Interest: None Declared

CRA toolbox: a MATLAB package for conditional robustness analysis of mathematical models in cancer systems biology

Lorenzo Tomassoni[* 1], Chiara Antonini[1], Paolo Valigi[1], Fortunato Bianconi[2]
[1]Information Engineering, University of Perugia, Perugia, [2]Information Engineering, Independent researcher, Montefalco, Italy

Secondary topic : Methodological developments for Systems Biology

Your abstract : In recent years, the analysis of complex biochemical networks has become increasingly important in cancer research for the development of targeted therapies. In this context, one of the most meaningful properties of such networks is cancer robustness, i. e. a quantitative measurement of the cells ability to maintain their malignant proliferation attitude against internal and external perturbations. In cancer systems biology this feature can be investigated through the robustness analysis of mathematical models. Robustness analysis consists in quantifying how much the temporal behaviour of a specific node is influenced by network perturbations.

The Conditional Robustness Algorithm (CRA) (DOI: 10.1186/s12918-015-0216-5) is a valuable technique to perform robustness analysis on a selected node, chosen as proliferation indicator (PI) of cancer disease.

Here we present the CRA Toolbox, an Object-Oriented MATLAB-based software package that implements and includes all the functionalities of CRA for Ordinary Differential Equation (ODE) models. The main features of the Toolbox are: (i) import of the mathematical model in Systems Biology Markup Language (SBML) format, (ii) selection of the ODE solver for model integration, (iii) perturbation of the parameter space using Linear Latin Hypercube sampling, (iv) choice of the reference node and the corresponding PI to compute, (v) selection of the method for the PI calculus, (vi) visualization and saving of all the results provided by CRA and (vii) easy to use Graphical User Interface (GUI) . CRA Toolbox has a modular and extendable architecture because it is designed according to different creational and behavioural design patterns. In more detail, the user can add novel functions for the definition and computation of the PI without altering the core structure of the software. The internal code is parallelized through the MATLAB Parallel Computing Toolbox in order to speed up the numerous routines. CRA Toolbox has been successfully applied in many nonlinear ODE models, comprising those in the above-cited paper (DOI: 10.1186/s12918-015-0216-5). The source and example code are freely available on http://gitlab.ict4life.com/SysBiOThe/CRA-Matlab.

Disclosure of Interest: None Declared

Comparison of lipid metabolism disruption in various brain tumors

Anatoly Sorokin[* 1], Vsevolod Shurkhay[1, 2], Stanislav Pekov[1], Evgeny Zhvansky[1], Igor Popov[1], Alexander Potapov[2], Eugene Nikolaev[3]

[1]Moscow Institute of Physics and Technology, Dolgoprudny, [2]N. N. Burdenko Scientific Research Neurosurgery Institute, Moscow, [3]Skolkovo Institute of Science and Technology, Skolkovo, Russia

Secondary topic : Multi-omics

Your abstract : It is known that the lipid metabolism reprogramming is one of the new hallmarks of cancer. Over the last decade, great progress was made in the understanding of the role of lipid metabolism in the progression of cancer. The main analysis of brain tumor was focused on glioblastoma multiforme (GBM), one of the most aggressive brain cancer.

We have collected over hundred untargeted lipidomic profiles from samples of unmodified brain and four brain tumors: GBM, astrocytoma, meningioma, and neurinoma. To increase the reliability of the analysis, we have combined our mass spectrometry profiles of lipids with data from transcriptomics and proteomics databases by graph analysis. We have identified subset of common features differ in unmodified brain and tumor samples. We have also shown that despite the presence of common features each type of tumor has its unique pattern. Detected patterns could be used for development of rapid diagnostics of the tumor progression for biomarker prediction and drug development.

Disclosure of Interest: None Declared

A mathematical model of the liver circadian clock linking feeding and fasting cycles to clock function

Aurore Woller[1, 2], Katharina Beuke[2], Hélène Duez[1], Bart Staels[1], Marc Lefranc[* 2]
[1]U1011, Institut Pasteur de Lille/Université de Lille/INSERM, Lille, [2]PhLAM, Université de Lille/CNRS, Villeneuve d'Ascq, France

Secondary topic : Quantitative Systems Physiology

Your abstract : To maintain energy homeostasis along the diurnal cycle, the liver relies on a circadian clock synchronized to food timing. Perturbed feeding and fasting cycles have been associated with clock disruption and metabolic diseases; however, the mechanisms are unclear. To address this question, we have constructed a mathematical model of the mammalian circadian clock, incorporating the intracellular metabolic sensors SIRT1 and AMPK [1]. The clock response to various temporal patterns of AMPK activation was simulated numerically, mimicking the effects of a normal diet, fasting, and a high-fat diet. The model reproduces the dampened clock gene expression and NAD+ rhythms reported for mice on a high-fat diet [2] and predicts that this effect may be pharmacologically rescued by timed REV-ERB agonist administration. However, it is known that besides intracellular factors such as AMP or NAD+, systemic factors such as insulin, glucagon, or free fatty acids (FFA) also can reset the clock. A natural question then is the relative importance of these different driving signals in synchronizing the clock hepatic clock. To address this question, we have constructed a simple 5-gene mathematical model driven by insulin, glucagon and FFA to study how well it can reproduce the clock phase shift observed when the feeding schedule is suddenly shifted by 12 hours [4]. We intend to eventually integrate all these stimuli in the same model to obtain a comprehensive mathematical description of how feeding/fasting cycles entrain the hepatic and other peripheral clocks.

[1] A. Woller et al., Cell Reports 17, 1087 (2016)
[2] Hatori et al., Cell Metab 15, 848 (2012)
[3] K. Eckel-Mahan et al., Cell 155, 1464 (2013)
[4] A. Mukherji et al., PNAS 112 E6683 (2015).

Disclosure of Interest: None Declared

QSP models versus empirical models for statistical clinical extrapolation: tools to aid decision making from early drug discovery to patient care

Cesar Pichardo-Almarza[*1], Neil Benson[1]
[1]Quantitative Systems Pharmacology, Certara, Canterbury, United Kingdom

Secondary topic : Quantitative Systems Physiology

Your abstract : Model based drug development [1, 2] proposes an integrated continuum of models to support drug discovery. According to this paradigm, models are envisaged as typically more mechanistic in the earlier part of the drug discovery process, such as Quantitative Systems Pharmacology (QSP) models and evolving to more empirical pharmacokinetic-pharmacodynamic (PKPD) representations as drugs move to the Phase II and III human trials. This reflects both a difference in the questions posed at the different stages of drug development and the availability of human specific data. For example, earlier in the development process questions are typically focussed around the best target or combination of targets in a given pathway and are often about confidence in mechanism. In contrast, the questions in Phase II and III are often more related to extrapolation of PKPD between cohorts and are more pharmaco-statistical. However, this important distinction is sometimes not clear and can lead to competing and perhaps mutually exclusive desire to produce QSP models that are both mechanistically informative and identifiable.

In the case of patient care, mechanistic models could be a “virtual” representation of an individual or a stratified patient population, considering its dynamic behaviour can reproduce similar results to statistical models based on clinical trials (e.g. hazard or survival models). QSP models have the potential of providing additional biological/physiological dynamic information to clinicians helping them to have a better understanding of the drug effect [3, 4], adherence [5] and disease progression [6]. This approach should help with the critical decision making process related to the current treatment of a given patient (e.g. continuation vs discontinuation, changing dose regime, etc.) and it is part of the rational of new progresses being made for model informed precision dosing [7].

This presentation will discuss this topic in the context of case examples drawn from cancer and pain drug discovery projects and a cardiovascular case related to patient care. We will show that QSP models can be used as tools for decision making, even while some uncertainty regarding all model parameters remains.

References

1. Clin Pharmacol Ther, 2013. 93(6).
2. Future Med Chem, 2014. 6(16).
3. Curr Pharm Des, 2016. 22(46).
4. CPT Pharmacometrics Syst Pharmacol, 2015. 4(1).
5. Front Pharmacol, 2017. 8: p. 635.
6. Front Physiol, 2016. 7: p. 238.
7. Clin Pharmacol Ther, 2017. 101(5).

Disclosure of Interest: None Declared

Identification of common and cancer type-specific gene expression programs according to cancer stage

Man-Sun Kim[*] [1] on behalf of Chungnam National University, Jeong-Rae Kim[2] on behalf of Chungnam National University, Yong Pyo Lim[3] and Chungnam National University
[1]Department of Horticulture, Chungnam National University, Daejeon, [2]Department of Mathematics, University of Seoul, seoul, [3]Department of Horticulture, , Chungnam National University, Daejeon, Korea, South

Secondary topic : Systems Medicine
Your abstract :

Cancer cells undergo various gene expression alterations according to their development and progression due to not only mutation accumulation in cancer cells but also complex interactions between cancer cells and their micro environmental factors. Identifying these gene regulation changes during cancer progression is very important for both understanding of cancer developing mechanisms and patients' prognosis. For some cancer types, several studies attempted to identify key gene expression changes for cancer progression. However, the pan-cancer analysis for identification of gene expression changes according to cancer development has not been addressed.

In this study, based on gene expression profiles and pathologic cancer stage data for 20 major cancer types obtained from about 6,500 individual patients, we identified genes that change according to each cancer type and across all cancer types. From the pan-cancer investigations, we found that cell cycle and p53 pathway genes are the most dysregulated genes during cancer development. Interestingly, we also found that the stage-dependent genes were significantly differentially expressed in different cancer types. We analyzed the commonalities and differences between cancer types and found that the 20 cancer types can be largely clustered into two cancer type classes. We further investigated the underlying mechanisms of how cancer development occurred differently in the two cancer type classes
Keywords: stage-dependent gene expression, systems biology, Pan-Cancer Analysis, bioinformatics

Disclosure of Interest: None Declared

A systems biology study of the effect of iodide on the development of foetal brain developement in rats

David Cohen[*1], Dalila Lebsir[1], Karine Tack[1], Marc Benderitter[2], Maâmar Souidi[1]
[1]PSE-Santé/SESANE/LRTOX, [2]PSE-Santé/SERAMED, IRSN, Fontenay-aux-Roses, France

Secondary topic : Systems Neurosciences

Your abstract : Following the nuclear accident at Fukushima Dai-Chi power plant, a single dose of potassium iodide (KI) (130 mg/tablet) against prolonged or repeated exposure or radioactivity might not be sufficient to protect the thyroid. The administration of a repetitive dose of potassium iodide may overcome this problem. Our group showed that repetitive administration of KI (1 mg/kg/day) for eight days offers efficient protection without toxic effects on adult male rats. However, the exact effect of repetitive KI on the developing foetus is not known especially on brain development. Nevertheless, a link between the impaired maternal thyroid status and a decrease in intelligence quotient has been noted.

In the current study, an *in utero* rat model has been subjected to repetitive KI administration over eight days. After administration of KI, transcriptomics was performed on tissue from the cerebellum, cortex, and thyroid. Transcriptomics of the cerebellum showed no presence of genes that are differentially regulated however, transcriptomics of the cortex showed 91 transcripts with assigned functions that are differentially regulated. Many of these transcripts can be associated with diseases including microdeletion, encephalopathy, frontotemporal dementia, holoprosencephaly, Spinocerebellar ataxia, and early-onset of familial Alzheimer disease. Also transcripts involved in axonogenesis, postsynaptic membrane complex and glial cell differentiation have been identified. For the thyroid, 60 genes (transcripts) have been found to be differentially regulated. Three genes are associated with encephalopathy, microcephaly and pontocerebellar hypoplasia. The other genes are involved in cancer.

These results indicate that KI might have a negative effect on the development of the cortex and thyroid. To better understand the regulation behind the differential expression of those genes involved in brain diseases and cancer, a network will be interfered using the R-package ShrinkNet. This network will be manually curated and be used for finding an explanation behind the effect of KI on the development of the cortex and thyroid of an *in utero* rat model.

Disclosure of Interest: None Declared

Prostate cancer: network analysis of molecular pathways and identification of novel biomarkers and drug targets

Elif Esvap[*1], Elif Ozkirimli Olmez[1], Kutlu O. Ulgen[1]
[1]Chemical Engineering, Bogazici University, Istanbul, Turkey

Your abstract :

Prostate cancer (Pca) is one of the leading cause of cancer deaths and second common cancer type in men after non-melanoma skin cancer. Early detection and treatment are crucial for high survival rates, which highlights the importance of identifying novel diagnostics and potential drug targets for Pca. Encoded by the kallikrein-related peptidase 3 (KLK3), prostate-specific antigen (PSA) is a protein almost only in prostate tissue and has been used as a biomarker for Pca for years. Although an increased PSA level is generally an indication of Pca, false negatives and positives are common. This shows the significance of identifying new biomarkers for Pca.

Biological networks provide novel information about biological function or complex cellular mechanism. In this study, two types of biological networks are constructed: Protein-protein interaction (PPI) and co-expression (CoExp). PPI network is reconstructed by choosing a core set of Pca proteins and adding their interactors obtained from BIOGRID, STRING, HPRD and IntAct databases by selective permissibility algorithm. Co-expression network is built using the Pca patient transcriptomics data from The Cancer Genome Atlas (TCGA). Several graph theoretical analyses such as network topology and functional enrichment are conducted, and putative biomarkers and drug targets are identified together with new disease modules and pathways. Using the systematic and integrative transcriptomics and interactomics approach, the putative transcriptional control mechanisms of Pca are deciphered. Consequently, the network medicine along with the multi-omics tools offers a multi-faceted platform for the investigation of prostate cancer, and will lead to design personalized therapeutics for Pca and other cancer types.

Disclosure of Interest: None Declared

In silico exploration of immunotherapeutics combinations in lymphoma

Adèle L'Hostis[* 1], Eulalie Landèche[1], Emmanuelle Bechet[1], Polina Kurbatova[1], Loïc Etheve[1], Jean-Pierre Boissel[1]
[1]NOVADISCOVERY, Lyon, France

Your abstract : Immunotherapeutics combinations in cancer appear as an attractive approach for the treatment of numerous cancers. However, comprehensive exploration of immunotherapeutic drug-paired combinations is impossible with conventional clinical trials because of the large number of combinations. *In silico* clinical trials is a solution to widely explore the potential drug combinations and identify those deserving to be pushed into clinical development.
The *in silico* clinical trial standard methodology relies on the Effect Model law, which establishes a functional connection between the drug effect on a biological system and its efficacy on clinical outcomes. It hence enables the prediction of the Absolute Benefit (AB) given by the treatment (or combination of treatments) of interest to each patient of a given population and the Number of Prevented Events (NPE) due to the treatment in this population.
We describe here an ordinary differential equations (ODE) model of the interactions of a lymphoma and immune cells, and the effect of the treatment on the cancer cells. The model includes a tumor microenvironment (TME) that is composed of large number of nonmalignant immune cells, including CD8+ tumor-infiltrating T cells, helper T cells, macrophages and natural killer cells. The model is applied to build a virtual population designed to account for the between patient variability thanks to different model parameters and initial conditions. The effect model is finally applied to the model outputs to compare the efficacy of three treatments on tumor progression: interferon-α, a tumor associated antibody b and their combination. Results suggest that the two interventions gave about the same NPEs and their combination efficacy is almost twice as efficacious, denoting additive effects of both interventions alone.

Disclosure of Interest: None Declared

In silico identification of possible pharmacological chaperones for neutral sphingomyelinase 2

Z. Begum Yagci[*1], Elif Ozkirimli Olmez[1], Kutlu O. Ulgen[1]
[1]Chemical Engineering, BOGAZICI UNIVERSITY, Istanbul, Turkey

Your abstract :

Neutral sphingomyelinase 2 (nSMase2) is an enzyme that hydrolyzes sphingomyelin to generate ceramide; a bioactive lipid involved in several cellular processes including inflammation, cell growth and apoptosis. NSMase2 has been suggested as a therapeutic target for several diseases such as Alzheimer's disease and cancer because of its possible role in exosome secretion, inflammation and cell growth arrest [1,2]. The known inhibitors of nSMase2 are scarce indicating that there is an urgent need for the discovery of novel inhibitors that target nSMase2.

The recent discovery of the crystal structure of the catalytic domain of human nSMase2 (PDB ID: 5UVG [1]) facilitated the computational analysis of this enzyme. In this study, we aim to identify the possible pharmacological chaperones of nSMase2 through an integrated workflow of structure-based pharmacophore modeling, virtual screening and molecular docking simulations. The available ligands in OTAVA database are screened at the binding pocket of nSMase2 via high-throughput virtual screening approach to determine the drug candidates for nSMase2. The stability and dynamics of the most promising nSMase2-ligand complexes are further examined by performing molecular dynamics simulations.

[1] Airola M V, Shanbhogue P, Shamseddine AA, et al. Structure of human nSMase2 reveals an interdomain allosteric activation mechanism for ceramide generation. Proc Natl Acad Sci . 2017;114(28):E5549-E5558. doi:10.1073/pnas.1705134114.
[2] Shamseddine AA, Airola M V, Hannun YA. Roles and regulation of neutral sphingomyelinase-2 in cellular and pathological processes. Adv Biol Regul. 2015;57:24-41. doi:https://doi.org/10.1016/j.jbior.2014.10.002.

Disclosure of Interest: None Declared

Unraveling the oligogenic potential of developmental disorders

Charlotte Nachtegael[* 1, 2], Sofia Papadimitriou[1, 2, 3], Nassim Versbraegen[1, 2], Guillaume Smits[1, 4, 5], Tom Lenaerts[1, 2, 3]

[1]Interuniversity Institute of Bioinformatics in Brussels, [2]Machine Learning Group, Université Libre de Bruxelles, [3]Artificial Intelligence lab, Vrije Universiteit Brussel, [4]Hôpital Universitaire des Enfants Reine Fabiola, Université Libre de Bruxelles, [5]Center for Medical Genetics, Hôpital Erasme, Bruxelles, Belgium

Your abstract : With the emergence of high-throughput sequencing and the increase of genomic data, insights into genetic diseases and their causality have evolved: when one gene is causative for multiple phenotypes, the influence of the genomic context cannot be denied. Moreover, the same phenotype can be linked to different genotypes, sometimes due to large genetic heterogeneity. These observations question whether bioinformatics approaches that purely focus on monogenic variant information have the capacity to identify sufficiently the genetic causes and their ability to link polygenic forms to a single phenotype (and vice versa).

In order to explore the monogenic to polygenic continuum, we studied patients suffering from developmental disorders from the Deciphering Developmental Disorders (DDD) cohort whose phenotype is already at least partially diagnosed. We explore through a high-throughput predictive method the combinations of the patients' variants in gene pairs in order to determine the diagnostic potential of these combinations for the observed phenotype. Filtering these results with the variant information of the parents allows for the extraction of those variant combinations in pairs of genes that are relevant, meaning that the combination is absent in the parents. The remaining combinations produce little modular networks, which are annotated with molecular information derived from biological networks like protein-protein interaction (PPI) networks, their variants and biological processes within the cell.

As we work with a highly heterogenous genetic background, but overlapping phenotypes, we try to establish a relationship between the networks and the diagnosis of patients with similar phenotypes with the hypothesis that a network-based approach will allow to connect the different genetic backgrounds with another layer of information. To reach this goal, we further study the networks properties and search for functional modules that could be attributed to specific phenotypes. We show here the results of this analysis with the ambition to reveal for the first time the potential for oligogenic explanations of the observed phenotypes in the DDD dataset.

Disclosure of Interest: None Declared

Metabolic characterization of metabolic syndrome: evidence from cross-sectional and longitudinal data

Blandine Comte[1], Stéphanie Monnerie[1], Cécile Canlet[2], Florence Castelli[3], Benoit Colsch[3], François Fenaille[3], Charlotte Joly[4], Christophe Junot[3], Natacha Lenuzza[5], Bernard Lyan[4], Jean-François Martin[2], Carole Migné[4], Mélanie Pétéra[4], Etienne Thévenot[5], Marie Tremblay-Franco[2], José A. Morais[6], Pierrette Gaudreau[7, 8], Estelle Pujos-Guillot[* 1, 4]

[1]Université Clermont Auvergne, INRA, UNH, mapping, Clermont-Ferrand, [2]Toxalim (Research Centre in Food Toxicology), Université de Toulouse, INRA, ENVT, INP-Purpan, UPS, MetaboHUB, Toulouse, [3]Laboratoire d'Etude du Métabolisme des Médicaments, DSV/iBiTec-S/SPI, MetaboHUB, CEA-Saclay, Gif-sur-Yvette, [4]Université Clermont Auvergne, INRA, UNH, Plateforme d'Exploration du Métabolisme, MetaboHUB Clermont, Clermont-Ferrand, [5]CEA, LIST, Laboratory for Data Analysis and Systems' Intelligence, MetaboHUB, Gif-sur-Yvette, France, [6]Division de Gériatrie, McGill University, Centre de recherche du Centre universitaire de santé McGill, [7]Centre de Recherche du Centre hospitalier de l'Université de Montréal, [8]Département de médecine, Université de Montréal, Montréal, Canada

Your abstract : Human health is a continuum of transitions, involving complex processes at multiple levels, and there is an urgent need to better characterize and predict disease development. In particular, the metabolic syndrome (MetS), defined as a cluster of cardio-metabolic factors including obesity, hypertension, dysglycemia, and dyslipidemia, and mostly affecting older adults often suffering from multiple chronic diseases, is now a public health challenge because of its growing prevalence. In the context of personalized medicine/nutrition, new tools are necessary to bring additional knowledge about MetS etiology, better stratify populations and customise strategies for prevention.

A nested case-control study on MetS was designed within the Quebec Longitudinal Study on Nutrition and Successful Aging (NuAge). It included 61 cases and 62 controls of similar age (68-82 y.o.), selected among the 853 men. Untargeted metabolomic/lipidomic approaches, available within the MetaboHUB French infrastructure [1], were performed on serum samples collected at recruitment 2003-2005 (T1) and 3 years later (T4). Data analysis were performed using reproducible online Galaxy workflows [2]. The metabolomic/lipidomic data were processed to identify specific signatures of MetS and its components, and study their stability over time. They were also integrated with phenotypic and detailed nutritional data available to better characterize sub-phenotypes.

Consistent cross-sectional and longitudinal data were observed with a wide range of metabolic biomarkers reflecting subject stability regarding MetS. However, a fraction of metabolic metabolites was significantly modified over time, suggesting a transition towards intermediate phenotypes associated with multiple metabolic changes.

The approach developed here, aiming to identify specific metabolic signatures, will open a door to a more comprehensive understanding of the metabolic phenotype resulting from the complex interplay between intrinsic and extrinsic factors. Altogether, this project will allow an improved description of MetS associated characteristics and will offer new tools for better patient stratification in elderly populations.

[1] http://www.metabohub.fr

[2] http://workflow4metabolomics.org

Disclosure of Interest: None Declared

Constraint-based modelling of redox couple perturbations anticipates cellular ageing and anti-ageing interventions

Alvar J. Alonso-Lavin[* 1], Djordje Bajic[2], Juan F. Poyatos[1]
[1]Systems Biology, Logic of Genomic Systems Lab (CNB-CSIC), Madrid, Spain, [2]Ecology and Evolutionary Biology, Yale University, Yale, United States

Your abstract : The metabolic stability-longevity theory of ageing proposes that the key factor determining lifespan differences across species is the robustness of their redox couple ratios in the face of random environmental and metabolic perturbations. In recent years, NAD+ has been receiving increasing attention as a key factor of senescence that can be used to reduce age-related phenotypes. Here, we explore the metabolic role of NAD+ in age by means of flux balance and constrained allocation flux balance analysis. First we introduce a redox perturbation of the NADH/NAD+ pair in a yeast metabolic network, and then we study the consequences of this perturbation for growth rate, energy metabolism and lifespan across different genetic backgrounds and chemical cues. Our results indicate that resistance to NADH/NAD+ imbalance can explain at least a third of the intraspecific variability in post-mitotic lifespan, and provide a computational tool for identifying potential nutraceuticals.

Disclosure of Interest: None Declared

Crosstalk between host miRNAs and the gut microbiome in neurodegenerative diseases

Charlotte Hewel[* 1], Julia Kaiser[1], Anna Wierczeiko[1], Aaron Zorn[1], Kristina Endres[2], Susanne Gerber[1] and Computational Systems Genetics Group
[1]Institute for Biology, JOHANNES GUTENBERG UNIVERSITY MAINZ, [2]Department of Psychiatry and Psychotherapy, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany

Your abstract : Neurodegenerative diseases such as Parkinson's Disease, Frontotemporal Dementia and especially Alzheimer's disease have increasingly come into the focus of biomedical research. However, many gaps still exist in our understanding of the etiologies of these diseases, as well as in our ability to provide effective treatments and early diagnostic options. So far, the research community has been unable to pinpoint a single causative factor for disease pathogenesis. It rather seems to be a complex polyfactorial meshwork of various genetic and non-genetic variables.
With that in mind, there has been mounting evidence over the last years that the gut-brain-axis is disturbed in neurodegenerative diseases and that there might be a direct connection between the host gut microbiome composition and neurodegeneration. It also has been shown in vitro, that host miRNAs are - in fact - able to pass through the bacterial cell wall, whereupon they downregulate specific bacterial target sequences. This gives further proof to the notion that the gut barrier, the host miRNA expression and the gut microbiota indeed correlate on an interspecies level.
Here, we present a bioinformatic pilot study with the purpose of identifying good candidate targets for possible interrelationships between host-expressed small RNAs and the gut microbiome in healthy subjects compared to patients suffering from neurodegenerative diseases. We approached the problem from three different perspectives: Firstly, we systematically investigated the differential expression of small RNAs in patients versus controls using publicly available datasets. Secondly, we screened available WGS-samples for human gut metagenomes for their bacterial composition via taxonomic labelling software.
And lastly, we focused on an interconnection between the previous two points. Herewith, we performed a target scan for possible target sites of the relevant miRNAs on the relevant bacterial genomes.
We will present first results and discuss current limitations of our approach as well as planned validation strategies and follow up studies with human cohorts, as well as in mouse models.

Disclosure of Interest: None Declared

Guarentee on the false discovery rate (FDR) and pairwise interactions in the penalized Cox model

Rémy Jardillier[*1], Laurent Guyon[1], Florent Chatelain[2]
[1]BIG/BCI UMR_S_1036, UGA/CEA/INSERM, [2]Gipsa-lab, Grenoble, France

Your abstract : Correlated to the fast decreasing of DNA/mRNA sequencing costs, there has been an increase of public available data for cancer in the last ten years. As an example, in the public American database TCGA, there are more than 500 patients diagnosed with kidney renal clear cell carcinoma (KIRC) for which both clinical data, including survival time of patients, together with microRNA sequencing data of the tumor are available. It makes new discoveries possible in term of prognostic biomarkers, and new methods are needed to analyze these high dimensional data (clinical and sequencing). The penalized Cox model is used to link survival times with gene expression levels and select the genes. Two main issues remain topical. First, there is a high false discovery rate in classical selection methods (lasso type penalizations), in particular as the number of tested genes is extremely larger than the number of followed patients. Second, synergies between genes exist and have to be taken into account to reach better prediction accuracy.

To tackle the first issue (selection accuracy), we developed a methodology based on permutation tests to compute a p-value for each gene. The lower the p-value, the higher the correlation between gene expression and patient's survival. Then, the selection is made after Benjamini-Hochberg correction for multiple testing. It is an improvement of the penalized Cox model in the sense that it aims to provide guarantees on the false discovery rate (FDR) among the selected genes.

To reach better prediction accuracy, pairwise interactions have been included in the linear model. The methods are illustrated on a renal cancer dataset from TCGA containing non-coding genes (microRNAs) expression levels (n=504 patients and p=462 microRNAs). For example, mir-223 is selected both in the model containing only main effects, and in the model with main effects plus interaction terms, in association with mir-130b. By separating the patients in two groups according to the expression level (lower than the quantile 40% and greater than the quantile 60%), we can compute the Kaplan-Meier estimator of survival curves. Then, the logrank test aims at computing a p-value measuring if the difference between the curves is significant. In the model with only main effects, the p-value for mir-223 is $6.83\ 10^{-6}$, and in the model with main effects with pairwise interactions, the p-value is $1.41\ 10^{-7}$. This shows the improved accuracy when synergies are taken into account.

Disclosure of Interest: None Declared

Transcriptional landscape of macrophage activations

Harukazu Suzuki* [1]
[1]Center for Integrative Medical Sciences, RIKEN, Yokohama, Japan

Your abstract: Classically and alternatively activated macrophages (M1 and M2, respectively) play distinct and important roles for microbiocidal activity, regulation of inflammation and tissue homeostasis. We have studied the transcriptional landscape of IFNγ (M1) or IL-4/IL-13 (M2) stimulated macrophages using promoter-level expression profiling by non-biased deepCAGE technology. Transcription factor (TF) binding motif activity analysis revealed that four out of five top active motifs, NFKB1_REL_RELA, IRF1,2, IRF7 and TBP, are commonly utilized but have distinct activity dynamics in M1 and M2 activation. We observe matching changes in the expression profiles of the corresponding TFs and show that only a restricted set of TFs change expression. Next we examined how *Mycobacterium tuberculosis* (Mtb) infection changes transcriptional landscape in M1 or M2 pre-activated macrophages. Cluster analysis uncovered significant numbers of genes prolonged their expressional changes. More importantly, Mtb-infection augmented cytokine-mediated M1 and M2 pre-activations. In summary M1 or M2 activations are operated in energy saving way and Mtb-infection in M1 or M2 pre-activation revealed interesting features from the view of host protection and subversiveness.

Disclosure of Interest: None Declared

Disentangling the complex impact of drug-induced liver injury compounds on IL-6 responses

Anja Zeilfelder[*1], Joep Vanlier[2], Marie Buck-Wiese[1], Marcel Schilling[1], Jens Timmer[2], Ursula Klingmüller[1]

[1]Systems Biology of Signal Transduction, DKFZ, Heidelberg, [2]Institute of Physics, Freiburg University, Freiburg, Germany

Secondary topic : Modelling Networks and Circuits

Your abstract : Interleukin-6 (IL-6) is a key effector cytokine with a central role in liver regeneration and inflammation. Recent findings link IL-6 signaling to Drug-Induced Liver Injury (DILI), an adverse drug reaction in a small population of individuals. Diclofenac (DCF) and acetaminophen (APAP), both regularly prescribed anti-inflammatory and analgesic drugs, are frequent causes of DILI. So far, the focus of research has been entirely on their direct hepatotoxic effect; however, these compounds could additionally affect liver regeneration and thereby might enhance liver injury. A systems biology approach is needed to disentangle the complex impact of DCF and APAP on IL-6 signaling in hepatocytes.

By applying quantitative immunoblotting and qRT-PCR we examined the dynamics of changes in IL-6 pathway components upon addition of IL-6 alone or in combination with DCF or APAP in the human hepatoma cell line HepG2 and in primary hepatocytes. In comparison to IL-6 alone, the combined treatment with DCF or APAP prolonged STAT3 phosphorylation and decreased its steady state level. While DCF drastically increased the amplitude of IL6-induced mRNA expression of the pathway inhibitor SOCS3, APAP only delayed its peak. Both treatments increased the mRNA expression of the iron regulator Hepcidin, however DCF to a higher degree than APAP. To disentangle theses complex effects we adapted our established dynamic pathway model of IL-6 signaling to the human context and integrated the acquired quantitative data. By applying L_1 regularization on the drug-induced changes in model reaction rates, we performed a structured analysis of possible points of interference of DCF and APAP in the molecular network. This analysis identified reactions that concern the maturation and stability of *SOCS3* mRNA and of the total SOCS3 levels as the most affected steps. These model-based hypotheses regarding the drug-induced effects were experimentally verified and included in the mathematical model. Whereas the extended model captured the impact of DCF and APAP on IL6-induced STAT3 phosphorylation and *SOCS3* mRNA expression, the impact on Hepcidin mRNA expression was not satisfactorily represented, suggesting that an additional input had to be considered. Our experimental and model-based studies revealed a critical additional role of the BMP/SMAD signaling axis. In sum, our approach provides a strategy to quantitatively assess drug-cytokine interactions and to unravel underlying cellular mechanisms.

Disclosure of Interest: None Declared

Lipidomics oriented metabolic model of adipocyte.

Zhixu Ni[* 1, 2], Georgia Angelidou[1, 2], Mike Lange[1, 2], Maria Fedorova[1, 2]
[1]Institute of Bioanalytical Chemistry, Faculty of Chemistry and Mineralogy, [2]Center for Biotechnology and Biomedicine, UNIVERSITY OF LEIPZIG, Leipzig, Germany

Secondary topic : Modelling Networks and Circuits

Your abstract : Obesity and associated predisposition to type 2 diabetes have been intensively studied over last decades and onset of insulin resistance was closely correlated with a low level chronic inflammation in expending adipose tissue (AT). Adipocytes are the major cell components of AT and one of the most insulin-responsive cell types. Dysregulation of adipocyte lipid metabolism and signal transduction lead to proinflammatory tissue phenotype, AT disfunction and development of insulin resistance. Lipid metabolism plays important role in adipocyte functional activities and thus a systems wide study of lipid metabolic and regulation functions in insulin sensitive and insulin resistant obese patients can significantly contribute the understanding of disease mechanisms. Previously published genome-scale metabolic models (GEMs) for adipocyte iAdipocytes1809 [1] provided a scaffold for further big data integration from different omics techniques. Here we used iAdipocytes1809 GEM for enrichment in data from high-throughput lipidomics analysis of insulin sensitive and resistance AT of obese patients. We extended and reconstructed the model into a lipidomics oriented network to analyze the metabolic and signaling function of different lipids. Enrichment and further GEM reconstruction will assist the early diagnostics of type 2 diabetes in obese patients using systems medicine approach.

[1] A. Mardinoglu et al., “Integration of clinical data with a genome-scale metabolic model of the human adipocyte.,” Mol. Syst. Biol., vol. 9, no. 1, p. 649, Jan. 2013.

Disclosure of Interest: None Declared

SUNDAY, OCTOBER 28
02:00 PM – 03:30 PM

Developmental Systems Biology - DEV

A method to predicting cell-fate determinants in cell differentiation

Andras Hartmann[*1], Satoshi Okawa[1], Gaia Zaffaroni[1], Antonio del Sol[1]
[1]Luxembourg Centre for Systems Biomedicine (LCSB), UNIVERSITY OF LUXEMBOURG, Esch-sur-Alzette, Luxembourg

Secondary topic : Developmental Systems Biology

Your abstract :

Differentiation is a complex process, where pluripotent, multipotent or progenitor cells evolve into more specialized cells. Although the detailed mechanisms and the pathways involved are not fully understood, it is generally accepted that a few transcription factors play a crucial role in determining cell fates (cell-fate determinants). Current tools for the inference of cell-fate determinants require comprehensive training or background data [1], and rely on precompiled datasets, which limit their predictions.

Here, we have implemented a computational pipeline for the prediction of cell-fate determinants from transcriptomics data that overcomes the above limitations. The method relies on the assumption that the progenitor cell phenotype is maintained in a metastable state by the opposing cell-fate determinants, which are part of interconnected feedback loops [2]. During binary cell-fate decisions, the equilibrium is shifted towards either of the two cell-fate determinants and the gene expression profile stabilizes in the corresponding daughter cell type. This is in line with the *"seesaw"* model for cell conversions that was proposed to describe the balanced expression pattern of the cell-fate determinants in the pluripotent state [3].

The validity of the method was confirmed in various binary cell differentiation examples in both human and mouse, where known cell-fate determinants were recapitulated. Moreover, the comparison with previously proposed methods showed a superior performance. We anticipate that further experimental validation will reinforce the generalizability of the method.

The method was implemented in R statistical language, and the web interface has been developed using the Shiny web technology, with all major browsers supported. A web application called SeesawPred has been made publicly available free of charge for academic non-profit use in order to guide differentiation experiments in stem cell research and regenerative medicine at http://seesaw.lcsb.uni.lu/.

1. Bian, Q., and Cahan, P. (2016). Computational Tools for Stem Cell Biology. Trends in Biotechnology 34, 993–1009.
2. Okawa, S et al. (2016). A Generalized Gene- Regulatory Network Model of Stem Cell Differentiation for Predicting Lineage Specifiers. Stem Cell Reports 7, 307–315.
3. Montserrat, N. et al. (2013). Reprogramming of Human Fibroblasts to Pluripotency with Lineage Specifiers. Cell Stem Cell 13, 341–350.

Disclosure of Interest: None Declared

Theory bridging cell polarities with development of robust complex morphologies

Silas Boye[*1], Steven Rønhild[1], Ala Trusina[1], Kim Sneppen[1]
[1]Niels Bohr Institute, University of Copenhagen, Copenhagen, Denmark

Your abstract: Despite continual renewal and damages, a multicellular organism is able to maintain its complex morphology. How is this stability compatible with the complexity and diversity of living forms? Looking for answers at protein level may be limiting as diverging protein sequences can result in similar morphologies. Inspired by the progressive role of apical-basal and planar cell polarity in development, we propose that stability, complexity, and diversity are emergent properties in populations of proliferating polarized cells. We support our hypothesis by a theoretical approach, developed to effectively capture both types of polar cell adhesions. When applied to specific cases of development - gastrulation and the origins of folds and tubes - our theory makes experimentally testable predictions pointing to the strength of polar adhesion, initial and boundary orientation of cell polarities, and the rate of cell proliferation to be major determinants of morphological diversity and stability.

Disclosure of Interest: None Declared

Erythroid differentiation displays a peak of energy consumption concomitant with glycolytic metabolism rearrangements

Angélique Richard[*] [1], Elodie Vallin[1], Caroline Romestaing[2], Damien Roussel[2], Olivier Gandrillon[1, 3], Sandrine Giraud[1]

[1]Laboratory of Biology and Modelling of the Cell, ENS de Lyon, Univ Claude Bernard, Univ Lyon, CNRS UMR 5239, INSERM U1210, Lyon, [2]Laboratoire d'Ecologie des Hydrosystèmes Naturels et Anthropisés,UMR 5023 CNRS, Villeurbanne, [3]Inria Team Dracula, Inria Center Grenoble Rhône-Alpes, Lyon, France

Your abstract : Previously, we have shown using single-cell transcriptomics a drop in LDHA, the main enzyme of the anaerobic glycolytic pathway, during the differentiation of chicken erythroid progenitors [1]. Since a switch from anaerobic glycolysis toward mitochondrial oxidative phosphorylation (OXPHOS) has been observed in different differentiation models, we investigated the possibility that such switch might be a driving force for erythroid differentiation.

We first analyzed from proteomic data [2] the expression level of 9 enzymes, including LDHA, involved either in glycolysis or OXPHOS, in self-renewing progenitor cells and at different differentiation time-points. Our results suggest that erythroid differentiation might be accompanied by an enhancement of the respiratory chain and the anaerobic glycolysis activities at 12h, followed by a strong decline of the glycolytic pathway and stabilization of OXPHOS at 48h.

To assess whether OXPHOS increased and anaerobic glycolysis decreased during erythroid differentiation, we measured lactate concentration, mitochondrial membrane potential and respiration rate of self-renewing and differentiating cells. Our findings show that at 12h-24h of differentiation energy demand rises, and then comes back to normal but might be supplied mostly by OXPHOS, instead of anaerobic glycolysis.

Finally, we also assessed LDHA role in erythroid progenitors self-renewal and the metabolic states changes. Inhibitory experiments showed that LDHA activity might influence the metabolic status of erythroid progenitors, and plays an important role in the maintenance of the self-renewal state.

Our results support the hypothesis suggesting that erythroid differentiation is associated with a metabolic switch from anaerobic glycolysis to OXPHOS. On the basis of these results and of our previous work [1], we propose that at a global integrated level, the concomitant increase in gene expression variability and metabolism rearrangements, possibly through modulation of epigenetic changes, might represent a causal driving force pushing the cells out of their self-renewing state and into their new differentiated state.

[1] A. Richard, L. *et. al*.. PLoS Biology, 14(12), 2016.
[2] M. Leduc,*et. al*. BioRxiv, 2018.

Disclosure of Interest: None Declared

Multi-scale modeling of planar cell polarity dynamics in planarians

Michael Kücken[1], Hanh Thi-Kim Vu[2], Karl Hoffmann[2], Anja Voss-Böhme[1, 3], Jochen Rink[2], Lutz Brusch[* 1]

[1]Centre for Information Services and High Performance Computing, Technische Universität Dresden, [2]Max Planck Institute of Molecular Cell Biology and Genetics, [3]University of Applied Sciences, Dresden, Germany

Your abstract : Polarity is a universal design principle of biological systems that manifests at all organizational scales. Mechanistic understanding of polarity pattern formation can be gained from dynamic pattern reorganization in response to perturbations. Here, we make use of the extreme body plan plasticity of planarian flatworms and quantify their polarity patterns from ciliary rootlet orientation in the epidermis [1].

Based on these whole-animal image data with subcellular resolution, we first define a dynamically diluted alignment model linking three processes: entrainment of cell polarity by tissue-scale cues, local cell–cell coupling aligning polarity among neighbors, and cell turnover replacing polarized cells by initially unpolarized cells [2]. Combining analytical and computational approaches using the software Morpheus [3], we find that neighbor coupling retards polarity pattern reorganization, whereas cell turnover accelerates it and derive an effective neighbour coupling strength [2].

Second, we consider a continuum model as large scale approximation of the cell-based model and apply it to combinatorial perturbation experiments of planaria. We find that the superposition of separate anteroposterior and mediolateral polarity fields can explain the observed reorientations of the global polarity field.

Overall, our study establishes a mechanistic framework for the multi-scale coordination of planar polarity in planarians and establishes the core PCP and Ft/Ds pathways as evolutionarily conserved 2D-polarization module [1].

[1] Vu et al., bioRxiv, 2018. doi:10.1101/324822

[2] Hoffmann et al., J R Soc Interface 14, 20170466, 2017. doi:10.1098/rsif.2017.0466

[3] Starruß et al., Bioinformatics 30, 1331, 2014. doi:10.1093/bioinformatics/btt772

Disclosure of Interest: None Declared

Emergent properties of stress-based regulation of growth in multicellular plant morphogenesis

Hadrien Oliveri[*1], Olivier Ali[1], Feng Zhao[2], Jan Traas[2], Christophe Godin[1]
[1]MOSAIC / RDP Laboratory, Inria, [2]RDP Laboratory, INRA, LYON, France

Secondary topic : Developmental Systems Biology

Your abstract : How thousands of individual cells control their local growth and collectively generate stable and repeatable (stereotypical?) macroscopic shapes is an open question. We address this question in plant morphogenesis, that relies on turgor-induced growth, regulated through rheological properties of the cell wall. In particular, it was proposed that cells may adapt these properties according to the mechanical stress they experience. In this scenario stress would provide a directional cue for the orientation in which cellulose fibres are deposited, leading to the anisotropic reinforcement of the walls.The dynamical behavior of such a system is nontrivial. In this work, we combine theoretical and numerical approaches to predict the emergent behavior of a stress-based regulation of growth. In particular, we show that this mechanism can maintain the typical plant growth modes, and amplify asymmetries. This is required to stabilize prolonged phases of asymmetric growth (stem or leaf growth) and, alternatively to escape a given growth regime and generate different levels of symmetry. Using the finite element models of a multi-layered tissue, we also provide new insights into the collective behavior of full stress-sensing structures, and nontrivial effects of multi-layered plant mechanics.

Disclosure of Interest: None Declared

Identification of gene morphogenetic activity functionalities through reachability analysis: the Arabidopsis thaliana flower morphogenesis case

Eduardo CHAIREZ-VELOZ[1], Carolina Elva CHÁVEZ-HERNÁNDEZ[2], Alberto SORIA-LÓPEZ[1], Elena R ALVAREZ-BUYLLA[3], Juan Carlos MARTINEZ GARCIA[* 4]
[1]Automatic Control Department, Cinvestav-IPN, [2]Phd Program on Biomedical Sciences, [3]Instituto de Ecología & Centro de Ciencias de la Complejidad, UNAM, [4]Automatic Control, Cinvestav-IPN, MEXICO CITY, Mexico

Secondary topic : Modelling Networks and Circuits

Your abstract : We are concerned here by transient dynamics in morphogenetic developmental patterns. More specifically, we explore the transitions between cell types understood as dynamical attractors of the underlying developmental gene regulatory networks. Taking as a case of study the floral organs specification in Arabidopsis thaliana, we illustrate a methodology intended to uncover the structural properties of reachability in abstract dynamical systems. The proposed methodology, based on an algebraic description of the gene regulatory network that coordinates floral organs specification (first described in Boolean discrete terms), addresses the uncovering of the functional role played by specific genes. In particular, it is shown that certain genes, for example, the Wushel(WUS) and Unusual Floral Organs (UFO) genes acquire, in the context of their collaboration in the regulatory network, sufficient properties for the determination of well-identified morphogenetic transitions (for instance, a suitable manipulation of WUS on petal primordium causes a transition to sepal primordium), showing that alterations in floral patterning can be caused by changing spatial cues in the meristem. Even if we do not establish the molecular nature of the manipulation, reachability analysis can give us some useful insights into the specific roll that individual genes have in the context of the network as a whole.

Disclosure of Interest: None Declared

Stochastic priming and spatial cues orchestrate heterogeneous clonal contribution to mouse pancreas organogenesis

Alexander Valentin Nielsen[*1], Hjalte List Larsen[2], Laura Martin Coll[3], Christopher V. E. Wright[4], Ala Trusina[1], Yung Hae Kim[3], Anne Grapin-Botton[3]

[1]Biocomplexity, Niels Bohr Institute - Copenhagen Univeristy, [2]DanStem - Larsen group, [3]DanStem - Grapin-Botton group, Faculty of Health and Medical Sciences - University of Copenhagen, Copenhagen, Denmark, [4]Cell & Developmental Biology, Vanderbilt university, Nashville, United States

Secondary topic : Modelling Networks and Circuits

Your abstract : Spatiotemporal balancing of cellular proliferation and differentiation is crucial for postnatal tissue homoeostasis and organogenesis. During embryonic development, pancreatic progenitors simultaneously proliferate and differentiate into the endocrine, ductal and acinar lineages. Using in vivo clonal analysis in the founder population of the pancreas here we reveal highly heterogeneous contribution of single progenitors to organ formation. While some progenitors are bona fide multipotent and contribute progeny to all major pancreatic cell lineages, we also identify numerous unipotent endocrine and ducto-endocrine bipotent clones. Single-cell transcriptional profiling at E9.5 reveals that endocrine-committed cells are molecularly distinct, whereas multipotent and bipotent progenitors do not exhibit different expression profiles. Clone size and composition support a probabilistic model of cell fate allocation and in silico simulations predict a transient wave of acinar differentiation around E11.5, while endocrine differentiation is proportionally decreased. Increased proliferative capacity of outer progenitors is further proposed to impact clonal expansion.

Disclosure of Interest: None Declared

Structured cell population dynamics applied to the early development of ovarian follicles

Frédérique Robin[*1], Frédérique Clément[1], Romain Yvinec[2]
[1]INRIA, Palaiseau, [2]INRA, Nouzilly, France

Secondary topic : Multiscale Systems Biology

Your abstract : The ovarian follicles are the basic anatomical and functional units of the ovaries, which are renewed from a quiescent pool all along reproductive life. Follicular development involves a finely tuned sequence of growth and maturation processes, involving complex cell dynamics. In their early stages of development, ovarian follicles are made up of a germ cell (oocyte), whose diameter increases steadily, and of surrounding proliferating somatic cells, which are layered in a globally spherical and compact structure. Here, we present two complementary modeling approaches dedicated to the first stages of a follicle development, starting with the exit from the pool of quiescent (primordial) follicles leading to growth initiation, and ending up just before the breaking of the spherical symmetry induced by the follicle cavitation (formation of the antrum cavity).

The initiation phase is described by joint stochastic dynamics accounting for cell shape transitions (from a flattened to a cuboidal shape) and proliferation of reshaped cells. We can derive the mean time elapsed before all cells have changed shapes and the corresponding increment in the total cell number, which is fitted to experimental data retrieved from primordial follicles (single layered follicle with only flattened cells) and primary follicles (single layered follicles with only cuboidal cells).

The next stages, characterized by the accumulation of cell layers around the oocyte, are described by multi-type structured models in either a stochastic or deterministic framework. We have designed a linear age-structured stochastic (Bellman-Harris branching) process ruling the changes in the number of follicular cells and their distribution into successive layers, as well as its deterministic counterpart (multi-dimensional McKendrick VonFoerster). We have studied the large-time behavior of the models and derived explicit analytical formulas characterizing an exponential growth of the population (Malthus parameter, asymptotic cell number moments and stable age distribution). We have compared the theoretical and numerical outputs of the models with experimental biological data informing on follicle morphology in the ovine species (follicle and oocyte diameters, layer number and total cell number) from the primary to the pre-antral stage.

Disclosure of Interest: None Declared

Evolutionary and Ecological Systems Biology - EVO

Duplication of homomeric proteins: retention of paralogs and evolution of protein-protein interactions

Axelle Marchant[* 1, 2], Alexandre Dubé [1, 2], Isabelle Gagnon-Arsenault[1, 2], Lou Nielly-Thibault[1], Yacine Seffal[1], Angel F. Cisneros[2], Christian R. Landry[1, 2]
[1]Département de Biologie, [2]Département de Biochimie, Microbiologie et Bio-informatique, Université Laval, Québec, Canada

Secondary topic : Evolutionary and Ecological Systems Biology

Your abstract : Protein-protein interaction (PPI) networks contain significantly more homomers than expected by chance alone (Ispalatov et al. 2005). The duplication of a homomer results in a pair of paralogs interacting with each other and two homomers. These pairs occur more frequently than expected by chance and homomers are enriched for duplicated genes, suggesting that they are more likely to be preserved after duplication. However, the evolutionary paths that follow PPIs after the duplication of self-interacting proteins and the consequences of these interactions are still poorly understood. Some scenarios suggest that this constrains the evolution of the paralogs while others suggest that it would favor their divergence (Kaltenegger and Ober 2015). Here, we experimentally studied the interactions of a large panel of paralogs derived from small scale (SSD) and whole genome (WGD) duplications in *Saccharomyces cerevisiae* to quantify these different scenarios. We first show that the mechanism of duplication has a strong impact on the pattern of self-interactions and interactions between paralogs. The evolution of the duplication of homomers seems to depend on the mechanism of duplication, which likely is due to the stoichiometric imbalance that follows SSDs in protein complexes. We show that homomeric paralogs can lose their association with each other through transcriptional divergence, which would free them from reciprocal physical constraints. We also find that older paralogs are more likely to form heteromers, consistent with their increased retention probability. We propose a model explaining the retention of paralogs from the duplication of homomeric proteins based on negative selection or neutral evolution alone. Altogether, our results bring new light on the evolution of gene duplicates and how the organization of protein interaction networks affect their evolution.

Disclosure of Interest: None Declared

Suboptimal transcriptional regulation contributes to the fitness cost following gene deletion in yeast

Karoly Kovacs[* 1], Zoltan Farkas[1], Dorottya Kalapis[1], Patrick Kemmeren[2], Frank C. P. Holstege[2], Richard Notebaart[3], Andreea Daraba[1], Zoltán Bódi[1], Karola Almási[1], Csaba Pál[1], Balázs Papp[1]
[1]BRC-HAS, Szeged, Hungary, [2]Princess Maxima Center for Pediatric Oncology, Utrecht, [3]Wageningen University & Research, Wageningen, Netherlands

Your abstract : Fitness loss following a single-gene deletion is generally attributed to the direct loss of the specific function of the deleted gene. Here we propose that an alternative mechanism, suboptimal physiological response to the genetic perturbation, can also contribute to the fitness loss. In order to experimentally test this scenario we performed a genome-wide screen for genes with suboptimally low transcript levels by manipulating their dosage in a slow-growing *Saccharomyces cerevisiae* single-gene deletion strain (*Δopi3*). Our screen revealed hundreds of suboptimally expressed genes and supports several predictions of the hypothesis. First, the frequency of suboptimally expressed genes is substantially higher in the perturbed genotype than in the wild-type. Second, most of the suboptimally regulated genes are not functionally related to the deleted gene. Furthermore, most suboptimally regulated genes are not in compensatory genetic interaction with the deleted gene either, suggesting that fitness loss cannot simply be explained by suboptimal regulation of genes providing functional backup. By combining our fitness data with the transcriptome profile of the deletion strain we found evidence that i) harmful downregulation, ii) lack of beneficial upregulation and iii) insufficient amount of beneficial upregulation can all result in suboptimally low expression level. Importantly, while lack of beneficial upregulation is the predominant mechanism, active misregulation also contributes to the fitness cost upon deletion. In sum, we demonstrated that the harmful fitness effect of a deletion can be attributed partly to the suboptimal transcriptional response. We hypothesize that this suboptimality is caused by the limited number of ways by which mutations rewire the genomic expression profile. Our work has important consequences for interpreting results of genetic perturbation studies.

Disclosure of Interest: None Declared

Functional alignment of genome-scale metabolic networks

Charlotte Ramon[*1,2], Joerg Stelling[1]
[1]Department of Biosystems Science and Engineering and SIB Swiss Institute of Bioinformatics, ETH Zurich, [2]PhD Program Systems Biology, Life Science Zurich Graduate School, Zurich, Switzerland

Secondary topic : Methodological developments for Systems Biology

Your abstract : Understanding the fundamental principles governing the evolution rate of proteins and the evolution of the phenotypic properties of species have been major concerns for the past 50 years. However, the approaches used in these two types of analysis do not allow to relate them and each approach suffers from disadvantages. First, most research that addresses the evolution rate of proteins uses nucleotide sequences to derive the evolutionary properties of proteins, where it is assumed that each protein operates in isolation from the rest of the organism. In contrast, only few studies tried to approach evolution using a systems biology view by investigating protein function in its context. Second, current methods for computing metabolic phenotypic similarities between pairs of microorganisms focus on indirect aspects, such as similarities in the carbon sources needed for growth or gene essentiality similarities. The major disadvantage of this approach is that it prevents deriving whether different parts of the network evolve at different rates.
Here, we propose to reconcile the fine-grained (protein) and coarse-grained (organism) view on evolution. To do so, we develop a framework for functional metabolic alignment to derive the phenotypic distance for each biochemical reaction between two metabolic networks. Each metabolic network is characterized by its perturbation profile using structural sensitivity analysis. The alignment then provides a one-to-one mapping between reactions in the two networks, the assigned sensitivity distance for each mapping and the average distance between two organisms. We studied the phenotypic evolution rate of 321 bacterial genome-scale metabolic models using 51’360 pairwise alignments. As previously observed, global sensitivity distance or phenotypic distance increase quickly at small genetic distances and saturate slowly at longer genetic distances. Also, sensitivity distances for unique reactions linearly decrease with their usage in the bacterial species. After correcting for this effect, the average evolution rate for the different metabolic functions and their evolution along time were observed to differ depending on the metabolic functions. For example, we could confirm that oxidative phosphorylation tends to evolve more slowly than other metabolic functions. Regulation of metabolic networks could be studied in follow-up methods to increase the coverage of the approach.

Disclosure of Interest: None Declared

On the evolvability of non-linear combinatorial regulation

Shruti Kaushal[1], Sumeet Agarwal[* 2]
[1]Mathematics, [2]Electrical Engineering, IIT Delhi, New Delhi, India

Secondary topic : Modelling Networks and Circuits

Your abstract : To characterise the powers and limits of evolution, one approach is to think of it as a form of learning over generations. Valiant [1] modeled the notion of evolvability as a form of learnability, using ideas from computational learning theory. Looking at a simple mathematical model of combinatorial transcription regulation, he showed that for binary-valued inputs/outputs, even though non-linear parity functions (such as exclusive-OR) are learnable, they are not evolvable, whereas linear conjunctions and disjunctions are. The evolution of transcription networks can also be studied via *in silico* simulation. For instance, Friedlander *et al.* [2] proposed a model which uses an intermediate stage of computation between inputs and outputs, and demonstrated the evolution of linear functions of continuous-valued inputs.

Both kinds of approaches illustrate the evolution of linear functions. However, in real signal transduction networks, functions such as exclusive-OR have been attested to. How have such mechanisms evolved? We sought to combine ideas from Valiant's framework and simulation-based approaches to evolvability to study this question.

We developed variants of the Friedlander *et al.* evolutionary algorithm, bringing in ideas from Valiant such as looking at binary-valued inputs/outputs and accordingly adjusting the fitness metric. One such variant can evolve non-linear functions such as exclusive-OR, in a fashion analogous to artificial neural networks. We conducted extensive simulations to study how the time complexity of evolving a particular kind of target function varies with model parameters. We show how regulatory models with multiple stages of computation between input and output (such as signal-transduction cascades) are essentially equivalent to neural network or deep learning models. Hence, by introducing non-linearity in the intermediate layer of computation in the Friedlander *et al.* model, we can evolve parity functions using their evolutionary algorithm. However, the time complexity of evolving these grows very rapidly with the number of inputs, in line with Valiant's result of the non-evolvability of such functions in polynomial time. So our analysis suggests that non-linearity in combinatorial regulation may only be feasibly evolvable for a small number of inputs, given reasonable constraints on the evolutionary algorithm; but that the nature of such evolvability can be understood in similar fashion to non-linear regression via neural networks.

Disclosure of Interest: None Declared

Understanding protein interactions - a semantic and Mycobacterium tuberculosis perspective

Sridhar Hariharaputran[*1]
[1]Lab 25, National Centre for Biological Sciences AND Indian Institute of Science AND Bharathidasan University, Bangalore, India

Secondary topic : Multi-omics

Your abstract : One third of Mtb gene products are not associated with functional data they have been categorized as unknown or conserved hypothetical proteins and tagged without any functional classification. Studying protein-protein functional interactions allows the analysis of an organism's functioning as an integrated system and enables the identification of the patterns and properties driving systems. It is not necessary that a functional interaction must involve a direct contact or physical interaction, it is a relationship between proteins contributing to cellular mechanisms that drives a particular protein to achieve its functions. The use of computational approaches and bioinformatics tools has opened a new route toward global analyses of whole genomes and investigating relationships between genes, providing the opportunity to look at genes within their context in the cell. For instance, in Mycobacterium tuberculosis (Mtb), the pathogen responsible for tuberculosis (TB) disease, there are 3933 protein-coding genes. Many of these genes are assumed to have essential functions, such as in DNA replication, transcription, translation, and cell-division but this annotation is only on the basis of homologues from other bacteria.

We use computational methods using sequence, structure and semantic information to understand the protein-protein interactions in Mtb and other species. We have been developing databases by integrating large information for generating large-scale networks and also tools to compare them using multiple information and for identifying the hubs, nodes and edges in the system and for identifying and understanding the drug-disease relationships. Databases (MyGO, MyCompare, MyPocket) deal with different information and helps to study the Mtb species.

Disclosure of Interest: None Declared

Methodological developments for Systems Biology - METH

The NormSys registry for modeling standards in systems and synthetic biology

Martin Golebiewski[*1], Wolfgang Müller[1]
[1]HITS gGmbH, Heidelberg, Germany

Secondary topic : Education for Systems Biologists

Your abstract : The rapid development of modern life science technologies allows data generation with increasing speed and complexity. In systems biology these data have to be stored, shared, processed, integrated, analyzed and compared. Hence, standards for formatting and describing experimental data, applied workflows and resulting computer models, all with their respective metadata, have become a critical issue, especially for interoperability of data from different sources.

Different stakeholders need to be engaged in the standardization process to incorporate their specific requirements: Researchers form academia and industries with their grass-roots standardization communities like the Computational Modeling in Biology Network (COMBINE: http://www.co.mbine.org), and representatives of standardization bodies such as the European CEN/CENELEC or the International Organization for Standardization (ISO), as well as scientific journals and research funding agencies. We drive and an coordinate standardization initiatives that aim at enhancing and harmonizing modeling standards by building a bridge between stakeholder groups and developing the means for transferring information about community-defined standards between them.

To survey standard formats for computational modeling in systems biology and related fields we have developed the web-based NormSys registry for modeling standards (http://normsys.h-its.org). It provides a single access point for consistent information about model exchange formats such as the Systems Biology Markup Language (SBML), CellML, the Systems Biology Graphical Notation (SBGN), the Simulation Experiment Description Markup Language (SED-ML), the Synthetic Biology Open Language (SBOL), NeuroML for neuroscience models, the Pharmacometrics, Markup Language (PharmML) and others. The publicly available platform not only lists the standards, but also compares their major features, their possible fields of biological application and potential use cases (including model examples), as well as their relationships, commonalities and differences. This NormSys registry provides a common entry point for anyone interested in modeling standards, especially for experimentalists, modelers and software developers who plan to apply the standard formats for their respective case of application, and serves them with detailed information, as well as with links to the webpages, specifications and web services of the formats.

Disclosure of Interest: None Declared

Sensitivity analysis of discrete models and application in biological networks

Gaoxiang Zhou[*1]
[1]UNIVERSITY OF PITTSBURGH, Pittsburgh, United States

Secondary topic : Modelling Networks and Circuits

Your abstract : Understanding sensitivity is an important step to study system robustness against perturbations and adaptability to the environment. Most of the previous sensitivity studies focused on the probabilistic Boolean networks, with all elements assigned a probabilistic update rule. But in this work, we model and investigate intra-cellular networks via discrete modeling approach, and we propose a framework to study sensitivity in these models. The discrete modeling approach assigns a set of discrete values and an update rule to each model element. The models can be analyzed formally or simulated in a deterministic or a stochastic manner. In the framework, we define element influence(activity) and sensitivity with respect to the state distribution of the modeled system. Previous sensitivity analysis approaches assume uniform state distribution, which is usually not true in biology. We perform both static and dynamic sensitivity analysis, the former assuming uniform state distribution, and the latter using a distribution estimated from stochastic simulation trajectories under a particular scenario.

In data flow diagram level, we start with a discrete model, apply predefined simulation scheme, compute element-to-element influences among the model elements. Then we extend the element update functions to include weights according to these computed influences. Adding weights to element update rules helps to generate a weighted directed graph, therefore benefits us in identifying key elements in the model and dominant signaling pathways that determine the behavior of the overall model. When studying cellular signaling networks, we are particularly interested in the response of elements to perturbations, as our goal is often to reach the desired model state via least number of interventions. Moreover, we have also applied our sensitivity analysis framework on pathway extraction and evaluation in the intra-cellular networks that controls T cells differentiation. Through this real biological model, we propose four different ranking algorithms to extract the most important pathways from a given source element to a given target element. We then evaluate these four algorithms using cross validation of corresponding extraction results. Our results show that, in different application occasions, different pathway extraction and evaluation algorithms should be adopted to help find "globally valid" or "globally effective" pathways.

Disclosure of Interest: None Declared

Prediction of infection outcome by computational modeling of Yersinia enterocolitica infection

Janina Geißert[1], Martin Eichner[2], Erwin Bohn[1], Reihaneh Mostolizadeh[* 3], Andreas Dräger[3], Ingo B. Autenrieth[1], Sina Beier[4], Monika Schütz[1]

[1]Institut für Medizinische Mikrobiologie und Hygiene, Universitätsklinikum Tübingen, [2]Epimos GmbH; Institute for Clinical Epidemiology and Applied Biometry, University of Tübingen, [3]UNIVERSITY OF TÜBINGEN, CENTER FOR BIOINFORMATICS TÜBINGEN (ZBIT), APPLIED BIOINFORMATICS GROUP, [4]UNIVERSITY OF TÜBINGEN, CENTER FOR BIOINFORMATICS TÜBINGEN (ZBIT), Algorithms in Bioinformatics, Tübingen, Germany

Secondary topic : Multiscale Systems Biology

Your abstract : The complex interplay of a given pathogen, its virulence and fitness factors, the host immune response and the presence and composition of the endogenous microbiome determine the course and outcome of gastrointestinal infection. An expansion of pathogens within the gastrointestinal tract implies an increased risk for the development of severe systemic infections, especially in patients receiving antibiotic treatment or in the immune-compromised state.

To predict pathogen expansion, gut colonization and infection outcome we employed a powerful measure of systems biology, i.e., the development of a computational model. For implementation and challenge of the model, oral mouse infection experiments with the enteropathogen *Yersinia enterocolitica* (Ye) were used. Our model is able to calculate the bacterial population dynamics during gastrointestinal infection and accounts for specific pathogen characteristics, the host immune capacity and colonization resistance mediated by the endogenous microbiome. First, we performed model parameter optimization based on the experimental data we obtained by the infection of a healthy host. Afterward, we challenged our model by adopting scenarios where either a microbiome was lacking (mimicking antibiotic treatment of patients), or where the immune response was partially impaired. The predicted Ye population dynamics based on these scenarios could be approved in experimental mouse infections.

Our model is able to provide new hypotheses about the roles of host- and pathogen-derived factors within this complex interplay and might be useful for future development of personalized infection prevention and treatment strategies.

Disclosure of Interest: None Declared

Identifiability in mixed effect models: the example of in vitro erythropoiesis

Ronan Duchesne[*1,2], Anissa Guillemin[1], Fabien Crauste[3], Olivier Gandrillon[1,2]
[1]Laboratory of Biology and Modelling of the Cell, [2]Team Dracula, Inria, Lyon, [3]Department of Mathematics, University of Bordeaux, Talence, France

Secondary topic : Quantitative Systems Physiology

Your abstract : Mounting evidence proves the importance of heterogeneity in biological processes. This increasing awareness has accompanied the development of Mixed Effect Models (MEM) in the last decades, to describe temporal data involving an important amount of variability. A MEM for a dynamical process consists in a mathematical model whose usually constant parameters are modeled by distributions of random variables. Different samples from these random variables model the repeated measurement of the same process on different individuals. It allows the model to adopt a whole range of behaviours, and to reproduce the distribution of an observed variable over time, instead of simply fitting its mean.

However, the choice of the parameter distributions might not be straightforward from raw data. More generally, it might be difficult to recover full parameter distributions from small datasets. This difficulty at estimating precise parameter values is known as identifiability issues. However, the question of how to assess, or even define, the identifiability of a MEM is a mostly open problem.

We address these issues through the example of a MEM for the dynamics of the *in vitro* erythropoiesis. Erythropoiesis is the process by which mature red blood cells are produced by the differentiation of immature progenitors in the bone marrow. These progenitors can either keep self-renewing, or engage into differentiation. A variety of mathematical models have focused on describing the dynamics of erythropoiesis *in vivo,* and we recently described a model focusing on the kinetics of cell populations growing and differentiating *in vitro.*

In this work, we build a MEM for the *in vitro* erythropoiesis based upon our previously described dynamical model. We use experimental cell counts of different cell populations, at regularly spaced time points during the course of erythroid differentiation to estimate model parameters.

The population of individuals to be fitted by the model is made of repeated samples of this experiment, each repetition giving qualitatively similar though quantitatively different results due to inter-individual heterogeneity.

We will illustrate the difficulty of fitting whole parameter distributions from such experimental datasets. Then, using artificial data, we will try to define identifiability for a MEM, and evaluate the experimental cost of making our model identifiable. Finally, we propose a simplified version of our model to match our identifiability criteria.

Disclosure of Interest: None Declared

Predictive models for protein sequences using knowledge distillation

Sandra Castillo[*1]
[1]Synthetic biology and metabolic engineering, VTT, Espoo, Finland

Secondary topic : Systems Biology for Synthetic Biology

Your abstract : Background: Deep learning has been shown to be a powerful tool for classification, removing the human bias in the creation of the features used in the machine learning models. There is a need for computational models that improve protein or gene annotations based on sequence data alone. The main limitation of deep learning algorithms is the big amount of labelled data necessary to create a good supervised predictive model.

The number of protein or gene sequences stored in databases is increasing rapidly due to the availability of low-cost sequencing techniques but only little high quality data is available for training a machine learning model. Information about protein or gene function, cellular localization or cofactor usage of the metabolic enzymes is essential for the understanding of the biology of the organisms and in areas like drug discovery, synthetic biology and metabolic modelling.

Methods: When the data is limited a useful way to improve the prediction power is producing an ensemble of many weak models. It leads to another limitation related to the model usability: the memory and resources needed by the ensemble model. Distilling the knowledge acquired by the group of weak models to a single model solves this problem (Hinton et al 2015).

In this work an ensemble of several weak deep learning models was trained using the experimentally reviewed annotations to predict protein cellular localization based on the protein sequence. Different model inputs were designed to make the model capture different aspects of the data: (1) ProtVec (Asgari et al. 2015) was used as a protein embedding for some of the models, (2) a total of 454 global protein features (such as proportion of the different aminoacids, proportion of charged aminoacids, ect) and (3) aminoacid features.

Results: The results show that the distilled model was able to capture the knowledge of the model ensemble making it superior to any of the individual models used in the ensemble model and also superior to a bigger model trained using experimentally reviewed and unreviewed data.

Conclusions: In this work we tried to alleviate the lack of biological data annotation by applying knowledge distillation technique to an ensemble of weak models, making the small amount of data suitable for deep learning approaches.

Disclosure of Interest: None Declared

JuFLUX: a one-stop-shop framework for 13C metabolic flux analysis

Martin Beyß[1], Salah Azzouzi[1], Axel Theorell[1], Peter Droste[2], Wolfgang Wiechert[1], Katharina Nöh[*1]

[1]IBG-1: Biotechnology, Forschungszentrum Jülich GmbH, Jülich, [2]Omix Visualization, Lennestadt, Germany

Secondary topic : Systems Biology for Synthetic Biology

Your abstract : ^{13}C Metabolic Flux Analysis (MFA) is the gold-standard approach to infer metabolic reaction rates (fluxes) in living organisms by means of computational modeling [1]. With that, ^{13}C MFA has become an indispensable systems biology tool in the design-build-test-learn cycle. After two decades of development, application of ^{13}C MFA still remains to be an expert approach that requires advanced experimental and computational expertise.

We present JuFLUX, a versatile computational platform for ^{13}C MFA that lowers the hurdles for executing complex computational modeling, simulation and evaluation workflows. By intuitive graphical plug-and-play-like workflow composition, but without resigning from universality, JuFLUX grants quick successes for beginners and a rich feature set for experts. JuFLUX features both, the classical isotopically stationary and the more recent isotopically non-stationary MFA variants [5]. Core functionalities reach from modeling over simulation (with the high-performance compute kernel 13CFLUX2, [4]) to parameter estimation with advanced state-of-the-art techniques [3]. ^{13}C MFA models are specified with the modern XML-based language FluxML, a FAIR-compliant modeling language. JuFLUX is developed in Java and C++ to be fast, platform agnostic and without the need for bindings to commercial software licenses.

Together with the visual modeling tool suite Omix [2], JuFLUX is a one-stop-shop for ^{13}C MFA. We demonstrate the unique attributes of JuFLUX with an application scenario where we develop, for the first time, strategies for the analysis of multiple-isotope labeling experiments.

References

[1] Niedenführ et al. 2015. Curr. Opin. Biotechnol. 34, 82–90. doi:10.1016/j.copbio.2014.12.003

[2] Nöh et al. 2015. Bioinformatics 31, 346–354. doi:10.1093/bioinformatics/btu585

[3] Theorell et al 2017. Biotechnol. Bioeng. 114, 2668–2684. doi:10.1002/bit.26379

[4] Weitzel et al. 2013 Bioinformatics 29, 143–145. doi:10.1093/bioinformatics/bts646.

[5] Wiechert et al. 2005. Adv. Biochem. Eng. Biotechnol. 92, 145–72. doi: 10.1007/b98921

Disclosure of Interest: None Declared

Design of isotopic labeling experiments for metabolic flux analysis: a ménage à trois

Martin Beyss[*1], Katharina Nöh[1], Axel Theorell[1]
[1]INSTITUTE OF BIO- AND GEOSCIENCES, IBG-1: BIOTECHNOLOGY, FORSCHUNGSZENTRUM JÜLICH GMBH, Jülich, Germany

Your abstract : In 13C Metabolic Flux Analysis (MFA) microorganisms are fed with specifically 13C-labeled tracers and the labeling incorporation of the label in the cellular intermediates is used for inference of the intracellular metabolic reaction rates (fluxes) [2]. The information gain of such isotope labeling experiments (ILEs) is determined by three factors, which are tightly interlinked: i) the tracer or tracer mixture ii) the observable metabolite fragments, and iii) the measurements' quality. In this context, the use of multiple tracers in so called parallel ILEs has become famous in recent years [1], since it increases the measurements-to-parameters ratio. This approach, which merely multiplexes the experimental efforts, is contrasted by a rational selection of tracer mixtures for a single ILE by means of information optimization. Which strategy is more effective for 13C MFA (in order to reduce the amount of redundant measurements) is still an open question. Furthermore, another limitation of existing design-of-experiment strategies is that only fixed measurement setups are considered. In a scenario where new analytical methods are to be developed, however, it becomes important to consider the selection of measurement information and tracers simultaneously.
Here we present a general approach towards determining the most beneficial ILE design taking all three information gain factors into account. To this end, we present a use case for Saccharomyces cerevisiae in combination with cutting edge GC-MS/MS technology. We determine informative fragments and labeled tracers, but also keep an eye on the cost factors, giving our work high practical relevance, not only in the field of 13C MFA. The overall goal of our ILE design efforts is to effectively derive a "just sufficient" amount of information on the fluxes.

References:
[1] Crown, Long, and Antoniewicz. Integrated 13C-metabolic flux analysis of 14 parallel labeling experiments in Escherichia coli. Metab. Eng. 2015; 24:151-158.
[2] Möllney, Wiechert, Kownatzki, de Graaf. Bidirectional reaction steps in metabolic networks: IV. Optimal design of isotopomer labeling experiments. Biotechnol. Bioeng. 1999; 66:86-103.

Disclosure of Interest: None Declared

Advances in Markov Chain Monte Carlo techniques for systems biology: shifting the limits

Axel Theorell[*1], Fredrik Jadebeck[1], Samuel Leweke[1], Katharina Nöh[1]
[1]IBG-1, Forschungszentrum Jülich, Jülich, Germany

Your abstract : The ultimate promise of Systems Biology is to provide a systematic, model-based approach to increase our understanding of the functional principles underlying living matter, in particular the regulatory mechanisms of organisms. However, the fulfillment of this task is complicated by our lack of knowledge on the precise model formulations together with incomplete and noisy measurements. Here we argue that an uncertainty-aware modeling paradigm is key, rather than relying on a single model instance or single set of parameters. In this context, Bayesian statistics is an advanced framework which recently gained popularity among computational biologists. At the very heart of the Bayesian approach are Markov Chain Monte Carlo (MCMC) sampling schemes that generate ensembles of models and parameter distributions from which inferences are made.
Application of MCMC sampling in Systems Biology models is particularly challenging due to the high dimensionality of the problems and the frequent occurrence of irregularly shaped parameter spaces. A sampling problem, common to stoichiometric modeling of cell metabolism, relates to parameters that are confined to convex polytopes, such as metabolic reaction rates. For our most challenging biological model systems, the sampling problems are computationally prohibitive, using existing technologies. In this contribution, we review the state-of-the-art MCMC samplers tailored for application in Systems Biology, explain their limitations and suggest improvements. In a range of practical examples, we compare existing samplers to new ideas and explore how the computational limits of sampling can be shifted further.

Disclosure of Interest: None Declared

Detecting treatment effects in preclinical neurotrauma models using univariate vs. multivariate statistics

Hristo Todorov[*1,2], Susanne Gerber[1]
[1]Faculty of Biology, Institute for Developmental Biology and Neurobiology , JOHANNES GUTENBERG-UNIVERSITY MAINZ, Mainz, [2]Fresenius Kabi Deutschland GmbH, Bad Homburg, Germany

Your abstract : Preclinical studies investigating the potential of a novel therapy are normally multivariate in nature, meaning that they include multiple correlated endpoints. Treatment effects are usually assessed by evaluating group mean differences in a series of univariate tests on each variable. Alternatively, a multivariate technique can be applied on a combination of the original variables. This approach has the advantage of taking the correlation between the variables into account but is associated with increased complexity of interpretation.
We addressed this problem through a series of computational simulations, allowing us to systematically evaluate the empirical type I error rate as well as the power of several univariate or multivariate techniques. We manipulated factors such as sample size, distribution of the dependent variables, homogeneity of variance and treatment effect size. The univariate approach of detecting treatment effects consisted of a series of independent analysis of variance (ANOVA) tests on each variable. The multivariate strategies included ANOVA tests on principal component scores obtained from the original variables, multivariate analysis of variance (MANOVA) tests on clusters of original variables grouped by principal component analysis (PCA) or MANOVA tests on groups of variables with repeated measures.
MANOVA tests on variables clustered by PCA were associated with the highest power under the majority of investigated conditions. However, this strategy also produced the highest type I error rate. Additionally, all methods seemed to be robust against violations of normality but unequal variance between control and treatment groups resulted in increased false positives rate and reduced power. Increasing treatment effects representing a linear dose response were detected by all methods with acceptably high confidence. In contrast, small effects present only in one group proved challenging for all strategies with power falling in the range of type I error rate.
Multivariate methods might offer an advantage in successfully detecting treatment effects in preclinical studies. However, the trade-off is higher false positives rate and increased complexity of interpretation. We will present a summary of our simulation battery as well as decision strategies for choosing the optimal framework for testing complex experimental setups in (medical) systems biology.

Disclosure of Interest: None Declared

Investigating functional connections in biological networks using transfer entropy: pitfalls and how to avoid them

Irina Surovtsova[*1], Jürgen Pahle[1]
[1]BIOMS, UNIVERSITY OF HEIDELBERG, Heidelberg, Germany

Secondary topic : Methodological developments for Systems Biology

Your abstract :

Inferring interaction networks from experimentally measured time series is of crucial importance for our understanding of the dynamics and function of complex biological systems. Recently, information-theoretic measures, such as transfer entropy, have been employed for detecting functional connectivity in dynamic multi-variate processes. Even though transfer entropy has a number of useful theoretical properties, in practice, the interpretation of the computed values can be very difficult.

We start with a very simple system, a linear vector auto-regressive model, as an initial test system. For this system, transfer entropy values can be calculated analytically, avoiding estimation errors. We investigate how indirect connections, unobserved variables and the lack of knowledge about the true Markov order (history length) of the system affect transfer entropy values. Then we explore ways of avoiding these problems and provide recommendations for the practical use of transfer entropy in systems biology.

We show how the unconditioned transfer entropy can be used for the detection of unobserved information sources in the system, and discuss the so-called "spurious transfer entropy" reported by different authors. Furthermore, we demonstrate that a conditional version of the transfer entropy, with appropriately chosen history lengths, can successfully reflect the underlying functional connections and their strengths. Combining these different versions of the transfer entropy allows for a more reliable inference of the causal structure of the system.

Finally, we use our findings to guide numerical analyses of non-linear versions of vector auto-regressive processes and models of cellular signalling systems, where analytical solutions cannot be given.

Disclosure of Interest: None Declared

The Systems Biology Graphical Notation: a standardised representation of biological maps

Vasundra Touré[1], Alexander Mazein[2], Adrien Rougny[* 3, 4], Andreas Dräger[5], Ugur Dogrusoz[6], Augustin Luna[7, 8], Nicolas Le Novère[9]

[1]Biology, Norwegian University of Science and Technology (NTNU), Trondheim, Norway, [2]European Institute for Systems Biology and Medecine, CIRI UMR5308, CNRS-ENS-UCBL-INSERM, Université de Lyon, Lyon, France, [3]Biotechnology Research Institute for Drug Discovery, National Institute of Advanced Industrial Science and Technology (AIST), [4]Com. Bio Big Data Open Innovation Lab. (CBBD-OIL), AIST, Tokyo, Japan, [5]Applied Bioinformatics Group, Center for Bioinformatics Tübingen (ZBIT), University of Tübingen, Tübingen, Germany, [6]Computer Engineering, Bilkent University, Ankara, Turkey, [7]cBio Center, Dana-Farber Cancer Institute, Boston, MA, [8]Cell Biology, Harvard Medical School, Boston, United States, [9]The Babraham Institute, Cambridge, United Kingdom

Your abstract : Visualization of biological processes plays an essential role in life science research. Diverse forms of diagrammatic representations, akin to circuit diagrams, have evolved without well-defined semantics potentially leading to ambiguous network interpretations and difficult programmatic processing.

SBGN is a standard developed to reduce ambiguity in the visual representation of biomolecular networks. It provides specific sets of well-defined symbols for various types of biological concepts. SBGN comprises three complementary languages: Process Description (PD), Activity Flow (AF), and Entity-Relationship (ER). PD allows representing the reactions underlying detailed sequential biochemical mechanisms, as found in metabolic pathways. AF is used to describe cascades of influences between activities of biomolecular entities, for which precise molecular mechanisms might not be known or be neglectable, as those of signalling and regulatory networks. ER permits representing independent interactions between features of biological entities, which avoids combinatorial explosions of represented biological states and interactions. SBGN-ML and the library libSBGN facilitate storage and exchange of maps.

SBGN is a community-driven effort coordinated by elected editors. Workshops, GitHub, and mailing lists are leading discussion platforms. Major research projects, databases, and software tools support SBGN.

Documents and source code are freely available at http://sbgn.org and https://github.com/sbgn. Contact: sbgn-discuss@googlegroups.com

Disclosure of Interest: None Declared

Image-based analysis of individual movement patterns of C. elegans

Jannis Hagenah[*] [1], Maximilian Hillemanns[1], Gereon Huettmann[2], Floris Ernst[1], Achim Schweikard[1]

[1]Institute for Robotics and Cognitive Systems, [2]Institute for Biomedical Optics, University of Luebeck, Lübeck, Germany

Secondary topic : Systems Biomechanics

Your abstract : During the past years, effort was taken to develop a general model of the neural system of C. elegans. The OpenWorm project defines one aim of its work as describing 80% of worm behaviour with one holistic model. However, there is a lack of knowledge about the individuality of C. elegans behaviour, especially concerning its locomotion. Thus, we followed an image-based approach to identify individual movement patterns. We used worm observation data from the WormBase data set and split the videos (about 15 minutes each) into sequences of 30 seconds each, resulting in about 30 video snippets. For each of these snippets, we extracted common locomotion features utilizing the WormTracker toolkit. Based on these features, we defined two worm locomotion descriptors that characterize the worm's movement in one video sequence: The mean midbody speed and the mean number of kinks over the snippet length of 900 frames, respectively. As a result, we derived a point cloud of about 30 data points for each examined worm individual, where each point describes the worm's locomotion during one short video sequence. To validate the feature descriptors, we examined whether an individual of the wildtype (JU345) can be distinguished from a mutant individual (VC12) with known abnormal locomotion. Using a two-sampled t-test ($p>0.05$) on the point clouds, we found that the mutant worm's locomotion was significantly different from the wildtype. Furthermore, we analysed whether 30 individuals of C. elegans (JU345, wildtype) can be discriminated from each other only based on their locomotion description. For each individual, we performed a two-sampled t-test ($p>0.05$) with each of the other 29 worms. We could show that in mean, each worm could be discriminated from 91.4% of the other individuals. The maximal number of worms that could not be discriminated from one worm was 2 out of 29. Our results indicate that the locomotion of C. elegans is highly individual and that most of C. elegans individuals of the same genotype develop specific movement patterns. This suggests that a generalized model of C. elegans locomotion behaviour might be insufficient and that the model should incorporate additional personalization parameters.

Disclosure of Interest: None Declared

A comparative study of modeling methods in systems biology using kinetic and polynomial approaches: a study on cooperative binding of Ca2+ on S100A4.

Fatima Jamal[*1], Don Kulasiri[1], Sandhya Samarasinghe[1]
[1]LINCOLN UNIVERSITY, NEW ZEALAND, Christchurch, New Zealand

Secondary topic : Methodological developments for Systems Biology

Your abstract : A COMPARATIVE STUDY OF MODELLING METHODS IN SYSTEMS BIOLOGY USING KINETIC AND POLYNOMIAL APPROACHES: A CASE STUDY ON COOPERATIVE BINDING OF CA^{+2} ON S100A4 PROTEIN.

Fatima Jamal [a], Don Kulasiri [a] and Sandhya Samarasinghe [a]
[a] Centre for Advanced Computational Solution (C-fACS), Lincoln University, Christchurch, New Zealand

Abstract**:**
The process of cooperative and allosteric binding of ligands to the macromolecules or proteins adds complexity to the ligand binding process studies. To understand these functions we have to look beyond the scope of the sequence of nucleotides encoding proteins required for a process and look into the network of interactive and interdependent regulatory networks as a system which allows certain regulatory expressions to happen. The expression of these networks in the form of computer models that extracts the topology of events occurring in the systems representing it in a systematic way makes the system easy to explain and predict. There are a number of ways in which a process or network can be modeled for easy explanations and understanding. In the current study we will be analyzing ligand binding interactions using two different modeling methods (1) BP (Binding polynomial) approach; (2) Kinetic modeling approach.
Human S100A4 protein, also known as Metastasin (Mts) is one of the most important and widely spread Ca^{+2} binding protein of S100 family, and it was the first S100 protein used in detection and screening of metastatic breast cancer cells. To understand the effect of Ca^{2+} binding and conformational change in S100A4, the reported structures in apo as well as Ca^{2+} bound form of S100A4 needs to be studied and compared using systems biology approach. The two modeling methods in Systems Biology will be compared and discussed in this poster, the comparison will be based on their application of the ligand binding interaction between Ca^{+2} and S100A4. The current study will help in extracting useful insights from the models revealing better interaction properties and biological significances of different parameters and concentration values on the ligand binding process along with a comparative analysis of the application of two different methods of modeling in systems biology.

Disclosure of Interest: None Declared

Inferring dynamics in metabolic networks via optimality principles: the interplay of constraints and trade-offs.

Nikolaos Tsiantis[*1], Julio R. Banga[1]
[1]BioProcess Engineering Group, Spanish National Research Council, IIM-CSIC, C/Eduardo Cabello 6, 36208 Vigo, Spain

Secondary topic : Modelling Networks and Circuits

Your abstract : Optimality principles have been used to explain the structure and behavior of living matter at different levels of organization, from basic phenomena at the molecular level, up to complex dynamics in whole populations. Most of these studies have assumed a single-criteria approach. In parallel, biological trade-offs have been widely studied in the context of metabolic networks, usually in the form of conflicting constraints, i.e. how the interplay of different functional limitations can provide understanding about a biosystem's behavior.
Here our aim is to integrate both perspectives via a robust computational framework based on multicriteria optimal control theory. Starting from a dynamic model of a biosystem and a set of possible cost functions, we present a methodology that produces a Pareto set (optimal trade-offs). These solutions can then be compared with experimental measurements to infer the optimality principle. Additionally, our approach enables us to focus on the effects of these trade-offs on the system's dynamics by observing the different balances along the Pareto front. Using the same framework, we also investigate the sensitivity of the Pareto front to the system's constraints and the impact of any inherent uncertainty. We illustrate this approach with two case studies regarding the dynamics of central carbon metabolism of *S. cerevisiae* and *B. subtilis* during diauxic shift experiments.

Disclosure of Interest: None Declared

Bayesian flux balance analysis; concepts and computation

Shirin Fallahi[*1], Hans J. Skaug[1], Guttorm Alendal[1]
[1]Mathematics, UNIVERSITY OF BERGEN, Bergen, Norway

Secondary topic : Modelling Networks and Circuits

Your abstract : In constrained-based metabolic modelling, the space of metabolic fluxes is described by an underdetermined linear system of equations satisfying steady state condition and a set of inequalities satisfying capacity constraints on the flux values. This space forms a convex polytope which is typically of high dimension and its shape is not regular due to tight or loose allowed bounds on the fluxes. Sampling this polytope uniformly is of interest and importance to obtain a better understanding of the cellular metabolism, however this task is challenging due to the features of the polytope. Sampling the polytope provides marginal distribution of the fluxes, whereas flux balance analysis (FBA) tries to compute a set of fluxes from the polytope optimizing an objective function. Here we briefly review existing methods to sample such a high dimensional and irregular shaped polytope uniformly. Moreover, a statistical alternative of the FBA in Bayesian framework is used. Currently available information about the fluxes such as limited capacity constraint, steady state condition and optimizing an objective function are encoded in the model through defining appropriate prior densities. The available flux measurements and uncertainty in the measurements are also integrated in the model through a likelihood probability density. We use the Bayes rule to make inference about the fluxes by approximately computing posterior probability densities using a Markov Chain Monte Carlo (MCMC) sampling technique known as Hamiltonian Monte Carlo (HMC). An example network is used to demonstrate how different constraints encoded in the prior change the distribution of the fluxes. We also show that how integrating flux data adjusts flux distributions and gives more accurate estimations of the fluxes.

Disclosure of Interest: None Declared

Modelling Networks and Circuits - MOD

Modelling the central carbon metabolism of three cancer cells using 13 C data

Roman Rainer[*1], Edda Klipp[1]
[1]Theoretical Biophysics, Humboldt-Universität zu Berlin, Berlin, Germany

Secondary topic : Methodological developments for Systems Biology

Your abstract : Ten percent of all colon cancer cases have an activating KRAS mutation. Cases with this kind of mutation do not respond to the usual drug treatment. KRAS mutated colon cancer cells have an accumulation of lactate, which is a potential option as a treatment target. We build a kinetic model to compare the KRAS cell line with two other common colon cancer cell lines to investigate the reason for the accumulation of lactate. The purpose of the model is to see if the differences of their central carbon metabolism are based only on enzyme concentrations or otherwise find potential modifications in enzymes. To achieve this goal we use flux data, metabolomics data, 13 C metabolomics data, and proteomics data. The model tracks carbon groups in glycolysis. We use the L1 regularization to find the differences in parameters for the cell lines.

Disclosure of Interest: None Declared

Heterodimer autorepression loop: a robust and flexible pulse-generating genetic module

Bruno Lannoo[1, 2], Enrico Carlon[1], Marc Lefranc[* 2]
[1]Institute of Theoretical Physics, KU Leuven, Leuven, Belgium, [2]PhLAM, Université de Lille/CNRS, Villeneuve d'Ascq, France

Secondary topic : Methodological developments for Systems Biology

Your abstract : We have investigated the dynamics of the heterodimer autorepression loop (HAL), a small genetic module in which a protein A acts as an autorepressor and binds to a second protein B to form an AB dimer. For suitable values of the rate constants, the HAL produces pulses of A alternating with pulses of B. By means of analytical and numerical calculations, we have showed that the duration of A pulses is extremely robust against variation of the rate constants while the duration of the B pulses can be flexibly adjusted. The HAL is thus a minimal genetic module generating robust pulses with a tunable duration, an interesting property for cellular signaling [1].

[1] B. Lannoo, E. Carlon and M. Lefranc, Phys. Rev. Lett. 117, 018102 (2016)

Disclosure of Interest: None Declared

Modeling the EGFR signaling pathway in gastric cancer

Elba Raimundez Alvarez[* 1, 2], Simone Keller[3], Gwen Zwingenberger[3], Karolin Ebert[3], Sabine Hug[1, 2], Dieter Maier[4], Birgit Luber[3], Jan Hasenauer[1, 2]
[1]Institute of Computational Biology, Helmholtz Zentrum München, Neuherberg, [2]Center for Mathematics, Chair of Mathematical Modeling of Biological Systems, Technische Universität München, Garching, [3]Institut für Pathologie, Technische Universität München, München, [4]Biomax Informatics AG, Planegg, Germany

Secondary topic : Methodological developments for Systems Biology

Your abstract : Background: Alterations in the human epidermal growth factor receptor (HER) family receptor family and HER-related signaling pathways are frequently observed in gastric cancer. Novel drugs targeting members of the HER family have shown mixed success in clinical trials. This is the case for cetuximab, an inhibitor of the epidernal growth factor receptor (EGFR), which has been approved in colorectal, non-small cell lung and head and neck cancer, but failed in a phase III trial for gastric cancer treatment. Understanding the connection between molecular mechanisms and treatment success of these therapies is highly valuable. Consequently, gaining mechanistic insights will facilitate a further identification of predictive biomarkers for patient stratification.

Methods: To understand the differences between the cetuximab responder cell line (MKN1) and the non-responder cell line (Hs746T), we developed a collection of mechanistic ordinary differential equation models for EGFR, ERK and AKT signaling, and their link to phenotypic properties, such as cell motility. These models describe different hypothesis and account for cell line specific mutation patterns and expression levels. We also explored further differences at a molecular level, i.e., cell line-specific reaction rates. We used the Matlab toolbox Data2Dynamics for modeling and parameter estimation. For the latter, we had a large set of molecular and phenotypic data collected under many different experimental conditions available.

Results: These models provide information on the relevance of individual molecular alterations and establish the link between the signaling state of the cell and cell motility. Among all the model topologies considered, our analysis revealed the importance of the mutation status of the MET receptor in the Hs746T cell line, and the role of PI3K mutations in the MKN1 cell line. We also predict differences between the cell lines, i.e., rate for receptor internalization and recycling. Highlighting the value and predictive power of these models, we validated predictions for new experimental conditions, such as silencing of MET or EGFR expression.

Disclosure of Interest: None Declared

Comparison of fluxome simulation and metabolome analysis using murine glioblastoma initiating cells.

Yoshitaka Inoue[* 1], Naoaki Ono[1, 2], Huang Ming[1], Md Altaf-Ul-Amin[1], Oltea Sampetrean[3], Hideyuki Saya[3], Shigehiko Kanaya[1, 2]

[1]Graduate School of Science and Technology, [2]Data Science Center, Nara Institute of Science and Technology , Ikoma, [3]Division of Gene Regulation, IAMR, Keio University School of Medicine, Tokyo, Japan

Secondary topic : Multi-omics

Your abstract : Drastic changes in metabolic system in tumor cells has been long discussed in order to understand behavior of cancer. For example, it is known as the Warburg effect that most of cancer cells prefer an aerobic metabolism such as lactate fermentation consuming a large amount of glucose, even in anaerobic conditions. Moreover, the balance between consumption and accumulation of Reactive Oxygen Species (ROS) has been considered as the key factor of cancer evolution since ROS may play either as inducer and as eliminator of tumor cells. Therefore, clarifying the relationship between metabolic mechanism and ROS is very important for further understanding of cancer.

However, it is difficult to understand the dynamics of ROS from metabolomics, because ROS can be produced in various ways through a wide range of reactions in a cell. For instance, NADPH oxidases, generally called the NOX family which produce active oxygen is known to be involved in many metabolic reactions, but we cannot measure the amount of ROS produced in each pathway. To address to this problem, in this study, we will develop a comprehensive model of metabolic fluxes in a cell and evaluate their behavior in different oxygen environment by comparing with metabolome and transcriptome experimental data using various cell lines of lung cancer tumor.

We developed the Flux Balance Analysis model based on the model Recon 2.2 developed by Neil S. et al. in 2016 which include 5324 compounds and 7785 reactions data and simulated to predict flux profiles under aerobic, microaerobic and anaerobic environments. Furthermore, we used the model to evaluate the changes in metabolic flux status with metabolomics profiles based on experimental results using the several clones of isogenic glioma-initiating cells (GICs) in a mouse model that show different metabolic phenotypes.

The results clearly showed the difference in the synthesis of metabolites in the glycolysis and the TCA cycle, such as lactate, malate, succinate and glycerol 3 phosphate etc. Finally, we will also discuss the effects on growth rates and efficiency of metabolic reactions in the different oxygen environments.

Disclosure of Interest: None Declared

An automatic platform for genome-scale metabolic model reconstruction and analysis

Djomangan Adama OUATTARA[*] [1], Clémence JOSEPH[1], Andrei BUNESCU[1], Joséphine ABI-GHANEM[1], Frédéric BEQUET[1]
[1]Metabolomics and Proteomics Technology Unit, BIOASTER, Lyon, France

Secondary topic : Multi-omics

Your abstract : Genome-scale *in-silico* metabolic models are inventories of the metabolic capabilities encoded by the whole genome. They are valuable tools to explore the intracellular and intercellular metabolic interactions, and mimic cell behavior [1]. They have gained an increasing interest in industry for the optimization of metabolite/protein production for example. However, to our knowledge, no platform exists to automatically reconstruct and explore *in silico* metabolic models with industrial requirements. The objective of this platform is therefore to deliver an automatic *in silico* pipeline for model reconstruction and exploration, strain design, prediction of metabolites/proteins production and microorganisms' interactions.

The platform relies on genome annotations available from database (e.g. ELIXIR consortium, KEGG) or obtained by genomics studies and software tools such as the COBRA and TIGER toolboxes [2, 3]. The integrated COBRA toolbox was simplified and only key modules necessary to curate and analyze models were automatized to match key industrial use-cases in the process of model reconstruction and analysis. The TIGER toolbox was also integrated to account for gene-protein-reaction (GPR) relationships and capture the metabolome regulation by the transcriptional activity. This allows co-integrating context-specific metabolomics, proteomics and transcriptomic expression data to improve model accuracy.

The platform is integrated a MATLAB toolbox that we designed to implement and deliver complex computational pipelines with industrial requirements.

1. Magnúsdóttir S., et al. Nature Biotechnology 35, no 1 (2017): 81-89
2. Heirendt L. et al. arXiv:1710.04038, 2017.
3. Jensen P et al. BMC Systems Biology no 5 (2011): 147.

Disclosure of Interest: None Declared

A subset selection method for accurate gene regulatory network inference of uninformative datasets

Deniz Seçilmiş[*] [1], Daniel Morgan[1], Andreas Tjärnberg[2], Torbjörn E. M. Nordling[3], Sven Nelander[4], Erik L. L. Sonnhammer[1]

[1]Department of Biochemistry and Biophysics, Stockholm University/SciLifeLab, Stockholm, [2]Department of Physics, Chemistry and Biology/Bioinformatics, Linköping University, Linköping, Sweden, [3]Department of Mechanical Engineering, National Cheng Kung University, Tainan, Taiwan, [4]Department of Immunology, Genetics and Pathology, Rudbeck Laboratory, Uppsala University, Uppsala, Sweden

Secondary topic : Multiscale Systems Biology

Your abstract :

The interactions among the components of a living cell that constitute the gene regulatory network (GRN) can be inferred from perturbation-based gene expression data. Such networks are useful for providing mechanistic insights of a biological system. In order to explore the feasibility and quality of GRN inference at a large scale, we used the L1000 data where approximately 1000 genes have been perturbed and their expression levels have been quantified in 9 cancer cell lines.

First we identified key properties of the datasets, i.e., signal-to-noise ratio (SNR) and condition number which we have shown to affect the performance of various inference methods. We found that all L1000 datasets have a very low SNR level causing them to be highly uninformative not suitable to infer accurate networks. Therefore, we have developed a gene reduction pipeline in which we eliminate the uninformative genes from the system using a selection criteria based on SNR until reaching an informative subset. The results show that our pipeline can identify an informative subset in an uninformative dataset, improving the accuracy of the network inference significantly.

Keywords: Data informativeness, Subset selection, Perturbation-based network inference, L1000

Disclosure of Interest: None Declared

Impact of network clustering methods on network-based pathway enrichment analysis tools

Miguel Castresana Aguirre[*1], Christoph Ogris[2], Erik L. L. Sonnhammer[1]
[1]Department of Biochemistry and Biophysics, Stockholm University/SciLifeLab, Stockholm, Sweden, [2]Department of Computational Biology, Helmholtz Zentrum München, Munich, Germany

Secondary topic : Multiscale Systems Biology
Your abstract :

Pathway enrichment analysis has turned into a key tool for a better understanding of the elemental biological relations between e.g. differentially expressed genes and biological pathways. Nonetheless, accuracy of the analysis is often decreased due to noisy and complex experimental gene sets. Gene sets are often made up of different gene clusters (modules) that may mask each others enrichment or depletion to a certain pathway, when performing pathway enrichment analysis on the gene set as a whole. To avoid this problem, we first cluster the gene sets into modules, and then apply pathway analysis techniques on the different modules with the aim to increase the sensitivity. The impact of clustering was benchmarked using different network-based pathway enrichment analysis tools, since they outperform simpler methods based on gene overlap. Three methods were used, BinoX (based on binomial distribution), NEAT (based on hypergeometric distribution) and a novel method based on resampling.

Disclosure of Interest: None Declared

Development of a flexible tool to compute biochemical reaction similarity

Taeyong Kim* [1]
[1]Biomaterials Lab, SAMSUNG ELECTRONICS, Suwon-si, Korea, South

Secondary topic : Quantitative Systems Physiology

Your abstract :

Background:
Computing chemical reaction similarity is pre-requisite for identification of enzymes for specific synthetic biochemical reactions, enzyme classification, mining specific inhibitors and other bioinformatics applications. Reaction similarity can be calculated by considering all the constituent substrates and products, often referred as reaction level similarity or considering only the transformation center at various degrees of neighborhood, referred as transformation level similarity. Various reaction similarity computing tools for specific applications are available. To maximize the prediction accuracy, molecular features such as fingerprints, similarity / diversity measures are employed. A single system integrating these diverse features along with comparative assessment is highly desirable.

Results:
Addressing above needs, we present SimCAL, an integrated system for calculating reaction similarity with novel features and capability to perform comparative assessment. SimCAL provides reaction similarity computation at both whole reaction level and transformation level. Users can also choose between four different fingerprint types and nine molecular similarity measures. In addition to these features, novel features such as stereo chemistry, mass, volume and charge are also included. Further, comparative assessment of these features is also enabled. In assessment with 3,688,122 reaction pairs with Enzyme Commission (EC) number from MetaCyc, SimCAL achieved area under curve (AUC) of >0.9. Benchmarking SimCAL with EC-BLAST and molecular signature based reaction similarity indicates strong correlation with the results.

Conclusions:
SimCAL is developed in java and is available as a standalone tool, with intuitive, user friendly graphical interface as well as a console application. With its customizable feature selection and similarity calculations, we intend to cater to wide audience interested in studying and analyzing biochemical reactions and metabolic networks.

Disclosure of Interest: None Declared

Modeling hormone-induced cell elongation in plant epidermis root cells using ODEs

Ruth Großeholz[*] [1], Nina Glöckner[2], Friederike Wanke[2], Stefan Scholl[3], Karin Schumacher[3], Klaus Harter[2], Ursula Kummer[1]

[1]Bioquant, Heidelberg University, Heidelberg, [2]Centre for Plant Molecular Biology, University of Tübingen, Tübingen, [3]Centre for Organismal Studies, Heidelberg University, Heidelberg, Germany

Secondary topic : Developmental Systems Biology

Your abstract : As sessile organisms, plants rely on growth to open up new sources of essential nutrients such as water or sunlight. However, since growth requires a lot of energy, it has to be tightly regulated. One class of hormones that is involved in the initiation and regulation of growth are brassinosteroids (BRs). BRs are a versatile group of plant steroid hormones that regulate a number of developmental and physiological processes including cell elongation. In particular, BRs are perceived in the plasma membrane by the receptor Brassinosteroid-insensitive 1 (BRI1). After ligand binding, BRI1 interacts with the co-receptor BRI1-associated kinase 1 (BAK1) and activates downstream signaling. In the fast BR response pathway in the plasma membrane BRI1 mediates the activation of the H+ ATPases resulting in membrane hyperpolarization and cell wall acidification. The latter, in turn, promotes cell elongation growth.

The ODE model we present here is a validated model that comprises the known components and steps of the fast BR response pathway in the plasma membrane of *Arabidopsis thaliana*. The model parameters have been fitted to dose-response data of the membrane potential in the elongation zone in response to different hormone concentrations. To account for parameter non-identifiability, a model ensemble of independent parameter sets was generated that describe the data equally well. The model ensemble has been validated with respect to the model's behavior in different root zones as well as in a mutant of an important negative regulator.

Furthermore, the model also comprises the BR-induced cell wall acidification and the subsequent wall swelling while accommodating the changing compartment sizes and scaling the reactions accordingly. Using this model, we are able to model an epidermis cell in the *A. thaliana* root from the young tissue at the very root tip, where it is only 8 µm long, to the final cell length of 220 µm. This elongation is hormone dependent even in the model, as the same parameterization of the model shows no response in absence of the hormone BR that can be rescued by the later addition of the hormone.

Disclosure of Interest: None Declared

Self-amplifying pulsatile protein dynamics without positive feedback

Rosa Martinez-Corral[* 1], Elba Raimundez[2], Yihan Lin[3], Michael Elowitz[4], Jordi Garcia-Ojalvo[1]
[1]Department of Experimental and Health Sciences, UNIVERSITAT POMPEU FABRA, Barcelona, Spain, [2]HelmholtzZentrumm münchen, Munich, Germany, [3]Peking-Tsinghua Center for Life Sciences, Peking, China, [4]Division of Biology and Biological Engineering, California Institute of Technology, Pasadena, United States

Secondary topic : Single-cell Systems Biology

Your abstract : Many proteins exhibit dynamic activation patterns in the form of irregular pulses. Such behaviour is typically attributed to a combination of positive and negative feedback loops in the underlying regulatory network. However, the presence of positive feedback loops is not always clear, as in the case of the yeast transcription factor Msn2, which is known to activate in a pulsatile manner. By taking the protein kinase A (PKA) system, a key Msn2 regulator, as a motivation, we show that irregular pulses can arise from the amplification of small fluctuations via a negative feedback loop alone. Further simplification of the model to two variables reveals that a combination of zero-order ultrasensitivity, differential timescales between the activator and the repressor, and an effective delay in the feedback is sufficient to generate a pulse in response to a perturbation. Furthermore, our results show that the same circuit topology can account for both activation and inactivation pulses, pointing towards a general mechanism of stochastic pulse generation that could be of broad relevance in biological systems.

Disclosure of Interest: None Declared

Perturbation-based gene regulatory network inference to reliably predict oncogenic mechanisms

Daniel Morgan[*1], Andreas Tjärnberg[2], Torbjörn Nordling[3], Erik Sonnhammer[1]
[1]DBB, Stockholm university, stockholm, [2]Department of Physics, Chemistry and Biology / Bioinformatics, Linkoping University, linkoping, Sweden, [3]Department of Mechanical Engineering, National Cheng Kung University, Tainan, Taiwan

Secondary topic : Systems Biomechanics

Your abstract : Cancer is known to stem from multiple, independent mutations, the effects of which aggregate to gain control of cellular activity. Many studies focus on isolated mutations crucial to disease progression. However, to understand the complex interplay between mutated genes, the gene regulatory network (GRN) need to be uncovered in order to give mechanistic insights. To make cancer GRNs actionable, the inference method must reliably infer links of high support. A reliable GRN was inferred from perturbation responses of genes known to have a role in human cancers but whose regulatory interactions are poorly known. Experiments were done on a human squamous carcinoma cell line. The false discovery rate of the GRN was controlled by nested bootstrapping using the NestBoot framework. The GRN´s topology was validated by measuring its ability to predict an independent dataset of the same genes but subjected to double perturbations. It agrees with many known links in addition to predicting a large number of novel interactions, a subset of which were experimentally validated.The inferred GRN captures regulatory interactions central to cancer-relevant processes and thus provides mechanistic insights that are useful for future cancer research.

Disclosure of Interest: None Declared

Computational modeling of the Hippo-YAP/TAZ pathway

Lilija Aprupe[*1], Sofia Weiler[2], Kai Breuhahn[2], Ursula Kummer[1]
[1]Centre for Organismal Studies Heidelberg, Heidelberg University, [2]Institute of Pathology, University Hospital Heidelberg, Heidelberg, Germany

Secondary topic : Systems Medicine

Your abstract : The Hippo pathway facilitates its biological function through the spatio-temporal regulation of the transcriptional co-activators *yes-associated protein* (YAP) and *WW domain containing transcription regulator 1 (*WWTR1 syn. TAZ). However, due to gradual changes in the subcellular localization of YAP/TAZ, which depends, among other factors, on cell density, precise conclusions concerning the dynamic Hippo pathway behavior under physiological and pathological conditions are challenging.

In order to shed more light on the control of Hippo signaling pathway, we utilized computational modeling methods to decipher how the dynamics of YAP/TAZ-translocation may affect the cellular response in cells grown at different cell densities. Thus, we created a comprehensive ordinary differential equation-based computational model of the Hippo pathway that captures known reactions and interactions. The model was set up using the software **CO**mplex **PA**thway **SI**mulator (COPASI). This mathematical model sufficiently describes how deregulation of the LATS1/2-YAP/TAZ pathway causes unconstrained cell proliferation, which is observed, e.g. in cancer cells.

Further modeling approaches are focusing on expanding the model and integration of experimental data into the model, such as, quantitative immunoblotting results of Hippo pathway components and dynamic localization data of YAP/TAZ derived from time-lapse microscopy.

The integration of quantitative experimental data into computational models (followed by iterative extension of the generated models) can explain how the dynamic fine-tuned regulation of YAP and TAZ may control distinct aspects of cell biology. In addition, new testable predictions and hypothesis about the Hippo signaling axis under physiological and pathological conditions can be generated.

Disclosure of Interest: None Declared

A subnetwork-based approach for studying concentration robustness

Alvaro Fletcher[*1], German Enciso[2]
[1]UNIVERSITY OF CALIFORNIA, IRVINE, Irvine, United States, [2]Mathematics, UNIVERSITY OF CALIFORNIA, IRVINE, Irvine, United States

Your abstract : Disturbances in the cellular environment can lead to variations in the chemical profile of the cytoplasm and result in deviations from homeostasis that are detrimental to the organism. In response, cellular networks have evolved to be robust to such perturbations but network complexity and the elusiveness of parameter values makes analysis difficult. Studying the network topology provides a way around this by delineating families of networks capable of exhibiting robustness based solely on their structure. Nevertheless, conditions for robustness have been studied mostly in the global context of the network and it is presumed that many of these conditions remain unknown. We propose that examination of a subset of reactions within the network suffices to show the presence of robustness. In particular, if a subnetwork inherits every possible steady state from its parent network, robustness in the subnetwork will extend to the entire network. We derive conditions that result in steady state inheritance for networks composed of at most two subnetworks. Additionally, we show that the steady state inheritance of one subnetwork extends to the other subnetwork as well. Lastly, we note an alternative submodule-based approach that extends robustness to the whole network based on species at the intersection of both subnetworks.

Disclosure of Interest: None Declared

Dynamical modelling of T cell co-inhibitory pathways to predict anti-tumour responses to checkpoint inhibitors

Celine Hernandez[* 1], Aurélien Naldi[1], Wassim Abou-Jaoudé[1], Guillaume Voisinne[2], Romain Roncagalli[2], Bernard Malissen[2, 3], Morgane Thomas-Chollier[1], Denis Thieffry[1]
[1]Institut de Biologie de l'Ecole Normale Supérieure (IBENS), CNRS UMR8197, INSERM U1024, Ecole Normale Supérieure, PSL Université, Paris, [2]Centre d'Immunologie de Marseille-Luminy, Aix Marseille Université, INSERM U1104, CNRS UMR7280, [3]Centre d'Immunophénomique, Aix Marseille Université, INSERM US012, CNRS UMS3367, Marseille, France

Your abstract : In recent years, it has been recognised that T cells often display a reduced ability to eliminate cancer cells and that expression of co-inhibitors at their surface accounts for their compromised function. Antibodies blocking the functions of these co-inhibitors (checkpoint inhibitors) have become standard treatment for metastatic melanoma (Simpson et al. 2013), leading to a revival in the study of T cell co-inhibitors. However, our understanding of the immunobiology of T cell co-inhibitors and of their harmful role during anti-tumour responses remains fragmentary. Despite some biochemical studies, a mechanistic understanding at the system-level of the modulation of T cell function by co-inhibitors has remained elusive.
To overcome these limitations, we aim at delineating the mechanisms through which co-inhibitory molecules, such as PD-1 and CTLA-4, impede T cell functions at the system-level. To reach this goal, we use computational methods to map and model TCR co-signalling pathways, and ultimately predict cell responses to perturbations.
First, we focused on the development of comprehensive annotated molecular maps (using the software CellDesigner, http://www.celldesigner.org) based on the curation of scientific literature, in parallel with automated queries to public databases and protein-protein graph reconstruction. Next, using the software GINsim (http://www.ginsim.org), these maps and protein networks are translated into a regulatory graph integrating current knowledge. The challenge is then to properly model concurrent intracellular processes, along with feedback control mechanisms. To cope with this complexity, we explored some network modules using a Rule-based formalism (Feret et al. 2009), in order to evaluate concurrent biological hypotheses and help specify logical rules recapitulating observed component behaviour back into the logical model. This model will be used to predict cell response to single or multiple perturbations, and thereby pave the way to the delineation of novel experiments, which will in turn be used to refine the maps and model.
This integrated system-level view of the mechanisms of action of key T cell co-inhibitors in cancer will further provide a rationale for designing and evaluating drugs targeting T cell co-inhibitory pathways in anti-cancer immunotherapy.

Disclosure of Interest: None Declared

Predictive modelling of the effect of heat stress time profiles on cell survival

Mohamed Tahar Ladjimi[*] [1], Darka Labavic[1], Marie Guilbert[1], François Anquez[1], Emmanuel Courtade[1], Benjamin Pfeuty[1], Quentin Thommen[1]
[1]University of Lille, Lille, France

Your abstract : Hyperthermia has been widely used as an anticancerous treatment. Inside cells, hyperthermia causes proteins to misfold and hence to lose their functionality, leading to a weakening of the cell. A standardized tool, the « Cumulative equivalent minute at 43°C » (CEM43) [1], determines the thermal doses from regression analysis in the specific case of rectangular time profiles of the hyperthermia treatment and is now widely used even for time varying profiles. We aim to revisit the concept of thermal doses in a mechanistic framework of signaling and regulatory network dynamics. We first extend a previous model of the heat-shock response network [2] to quantitatively account for the survival response of Hela cells to rectangular heat shocks of varying duration and temperature [3], consistently with the CEM43 model. Such network model featured with specific dynamical properties further allows us for systematic and quantitative study of the influence of the temporal profile of the thermal protocol on the survival response. The model predicts that the asymmetry profile of the hyperthermia treatment has a strong effect on survival: a fast temperature rise followed by a slow decay can be twice more lethal than a slow rise followed by a fast decay with the same CEM43 dose. Such « asymmetry effect » has been experimentally confirmed by combining an accurate monitoring of the temperature and real-time measurements of growth rate and death rate in Hela cell culture. A mathematical analysis of a reduced model reveals that the dynamics of HSP-dependent repair of misfolded proteins plays a critical role in this process.
Key words : heat shock response, cell death, thermotolerance, signaling pathways, mathematical modelling, CEM43.
[1] : Sapareto SA and Dewey WC, « Thermal dose determination in cancer therapy », International Journal of Radiation Oncology Biology Physics, 1984, 10, 787 800.
[2] : Sivéry A, Courtade E, Thommen Q, « A minimal titration model of the mammalian dynamical heat shock response », Physical Biology, 2016, 13
[3] : Gerner EW, Boone R, Connor WG & al, « A transient thermotolerant survival response produced by single thermal doses in Hela cells », Cancer Research, 1976, 36, 1035-1040.

Disclosure of Interest: None Declared

Reconstruction of whole-genome metabolic model of Atlantic salmon Salmo salar (SALARECON)

Maksim Zakhartsev[*1], Jon Olav Vik[1], Fabian Grammes[1] and Digital Salmon
[1]NORWEGIAN UNIVERSITY OF LIFE SCIENCES (MNBU), Ås, Norway

Your abstract : Introduction: Atlantic salmon *Salmo salar* is Norway's main livestock and the biggest export commodity after the oil. Currently, the plant feedstock is the main feed for the farming of salmon, consequently, it influences both growth rate and quality of the fish biomass. The whole-genome (WG) metabolic model of *S.salar* (SALARECON) will allow multifactorial optimization of the fish growth conditions by means of a diet for the application in salmon farming. Special interest will be paid to the optimization of fat yield and growth limitations due to dietary amino acids.
Methods: The genome and metabolic information are available at NCBI and KEGG. The SALARECON is the stoichiometric model that describes the steady-state growth of the biomass. The reconstruction workflow includes (i) Gene-Protein-Reaction associations (GPRs) using in-house SAPP system; (ii) network setup and network topological analyses; (iii) Flux Balance Analysis for optimization of the network using Insilico Discovery package. The model allows integration of high-throughput experimental omics-data (transcriptomics, proteomics, metabolomics).
Results and Discussion: The model integrates all important biochemical reactions/pathways that lead to polymerization of major biomass constituents: proteins, carbohydrates, fats/lipids, polynucleotides. The modelling methodology is based on energy-centric approach because energy- and redox-balances in different subcellular compartments play a central role in coupling and harmonizing activities of different metabolic modules and pathways. The energy costs for the ion balance is one of the main contributor to the maintenance costs. The model will be optimized for two osmotic scenarios: fresh and sea waters.
Currently, the SALARECON integrates 356 transformer steps (performed by products of 1017 genes), 2293 balanced compounds belonging to 59 pathways which are allocated in 3 compartments. For the network reconstruction, the in-house developed SAPP system is used to predicts GRP associations as well as subcellular compartment localizations of the corresponding biochemical reactions.
The model aims to optimize a whole range of possible diets of farmed salmon. The exact formulation of the biomass composition (model's output) defines the input fluxes through the network of reactions, which are compared with experimentally measured dietary requirements. The model is validated using the variety of experimental omics-data.

Disclosure of Interest: None Declared

Stochastic binary switching behavior of nonlinear neuron explains different responses to same stimulation in C. elegans

Yuishi Iwasaki[*1], Kota Abe[1]
[1]Department of Mechanical Systems Engineering, Ibaraki University, Hitachi, Japan

Secondary topic : Modelling Networks and Circuits

Your abstract : Experimental background: The nervous system of C. elegans consists of 302 neurons and about 170 neurons locate in the head region (central nervous system). The synaptic connectivity is completely determined. Our research collaborators developed a 4D imaging system to measure the neural activities in the central nervous system [Toyoshima et al., PLoS Comput. Biol., 2016]. In the whole-brain imaging data of C. elegans, some neuron groups show different responses (nearly in anti-phase) to periodically added same stimuli. The different responses in the neural activity can be explained by dynamical property of a single neuron or/and that of neural network. From the electrophysiological experiments, it is known that several neurons in C. elegans have nonlinearity in electrical property. In this presentation, therefore, we focus on the former mechanism.

Mathematical methods and results: To study about neural response to the stimulation, neural activity of a model neuron is simulated. Neural dynamics is governed by its own electrical property (current-voltage curve) which is determined by the electrophysiological date in C. elegans. We confirmed that our simulations reproduce well the experimental results. In this presentation, stochastic fluctuation is introduced into the neural system. This noisy dynamics of neuron is calculated by a stochastic differential equation. If several steady-state solutions (bistable nullclines) exist in the current-voltage curve, the model neuron shows stochastic binary switching behavior at appropriate noise intensity. That is, the neuron stochastically jumps from one stable state to the other stable state by noise boosting. This phenomenon is known as "stochastic resonance" which is not experimentally reported in C. elegans. We consider that the stochastic binary switching is a possible trigger of the different responses to the same stimulation.

This phenomenon is a random event. To quantitatively understand when the stochastic binary switching occurs in the neuron, furthermore, we calculate the probability density function of stochastic neural activity, that is, the probability that neuron stays at any given state at any given time. The probability density function has two sharp peaks at the stable states. Fokker-Planck equation is used to calculate the time evolution of the probability density function. We refer to the noise intensity dependence on change of the probability density function. This work was supported by CREST, JST.

Disclosure of Interest: None Declared

Mathematical modelling of pathway interactions and activation dynamics to predict cell responses to chemotherapeutic treatments in breast cancer cells

Laura Tuffery[*1], Dirk Fey[1], Melinda Halasz[1], Boris N. Kholodenko[1], Walter Kolch[1] and Cancer dynamics and modelling
[1]System Biology Ireland (UCD), Dublin 4, Ireland

Secondary topic : Methodological developments for Systems Biology

Your abstract : Breast cancer is the most common cancer among women affecting about 1 in 8 women during their life[1]. Standard treatment is surgery combined with chemotherapy such as Doxorubicin[2]. Unfortunately, chemotherapy is only working for 25 to 50% of the patients showing a need to predict the patient's response[2]. Chemotherapeutic drugs are known to activate apoptosis via the activation of JNK, p38 and p53 pathways[3]. However, little is known about the interaction between these pathways.

My hypothesis is that dynamic behaviour and network interactions between JNK//p38 and p53 confer drug sensitivity and resistance. My project merges molecular and computational approaches to answer two questions:
-What are the activation dynamics and underlying network interactions?
-Can a mathematical model of network predict drug-responses?

For this study, I compared MCF10A cells, a non-cancerous cell line, with five breast cancer cell lines. The level of cell death induced by Doxorubicin treatment was measured via flow cytometry and compared with molecular response monitored via Western blots. The comparison of MCF10A cells response with other cancer cells lines showed differences on two levels: network topology and activation dynamics. Using ordinary differential equation (ODE), I established a predictive model of pathway activation that showed a strong correlation between experimental data and the simulated outcome of Doxorubicin treatment in MCF10A cells. Furthermore, my mathematical model outlined an interaction between the stress-activated pathways (JNK and p38) and the DNA-damage pathway (p53).

Currently, I am integrating the genetic alteration of cancer cell lines in my model by modulating the expression parameters of my initial ODE system[4]. Hopefully, this will explain the differential pathway interaction and dynamics between cell lines with different mutation patterns. My final aim is to predict treatment response of breast cancer cells in patients to develop personalised treatment strategies.

1.Cancer Research UK. http://www.cancerresearchuk.org/
2.Bonotto M. *et al.* Treatment of Metastatic Breast Cancer in a Real-World Scenario: Is Progression-Free Survival With First Line Predictive of Benefit From Second and Later Lines? *Oncologist*
3.Fey D. *et al.* Signalling pathway models as biomarkers: Patient-specific simulations of JNK activity predict the survival of neuroblastoma patients. *Sci Signal*
4. Fey D. *et al.* On the personalised modelling of cancer signalling, *IFAC-PapersOnLine*

Disclosure of Interest: None Declared

The Human Whole-Cell Modeling Project

Arthur Goldberg[*] [1], Balazs Szigeti[1], Yosef Roth[1], John Sekar[1], Saahith Pochiraju[1], Yin Hoon Chew[1], Jonathan Karr[1]
[1]Icahn Institute and Department of Genetics & Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, United States

Secondary topic : Single-cell Systems Biology
Your abstract : Whole-cell (WC) computational models of human cells are a central goal of systems biology. WC models could help researchers understand cell biology and help physicians treat disease. Ongoing technological advances in experimentation and modeling are enhancing the feasibility of WC models. However, progress toward WC models remains slow.
To identify the bottlenecks to WC modeling and develop a long-term plan to achieve human WC models, we surveyed the biomodeling community, reviewed the literature, and reflected on our experience prototyping WC models of bacteria. We identified four major bottlenecks: a) inadequate experimental methods and data repositories; b) inadequate tools for designing, describing, simulating, calibrating, and validating large models; c) few models of individual processes that can be combined into WC models; and d) insufficient coordination within the biomodeling community.
Further, we propose a project, termed the *Human Whole-Cell Modeling Project,* which would overcome these bottlenecks and achieve the first human WC models. The cornerstones of the project include developing computational technologies for scalably building and simulating models, developing standard protocols and formats for collaborative modeling, collaboratively building models as a community, and focusing on a single cell line. We invite the community to join this exciting and ambitious effort.

Disclosure of Interest: None Declared

Modelling the cytosolic [Ca2+] responses induced by Shigella invasion in epithelial cells

Roberto Ornelas-Guevara[*] [1], Benjamin Wacquier[2], Geneviève Dupont[2], Virginia González-Vélez[3]

[1]Process Eng. Posgraduate program, Universidad Autonoma Metropolitana, Mexico city, Mexico, [2]Unité de Chronobiologie Théorique, Université Libre de Bruxelles, Brussels, Belgium, [3]Dpto Ciencias Basicas, Universidad Autonoma Metropolitana, Mexico city, Mexico

Your abstract : Shigellosis is an important problem of public health worldwide. It is mainly caused by the ingestion of contaminated food or water contaminated with *Shigella.* After its ingestion, this bacterium invades the colon and causes an intense inflammatory reaction, leading to destruction of the epithelial tissue. During cell invasion, *Shigella* induces atypical Ca^{2+} signals, but its role in invasion has remained unclear and poorly studied (Tran Van Nhieu *et al.,* 2013).

It is well known that every cell type uses Ca^{2+} as a second messenger to control a wide array of cellular functions, including reorganisation of the cytoskeleton, inflammatory responses and cellular death (Sun *et al*., 2017). The perturbation of cellular Ca^{2+} homeostasis caused by *Shigella* facilitates the entrance of the bacteria and its dispersion to adjacent cells. This further leads to apoptosis and destruction of the intestinal epithelium. The bacterium induces local responses, described as an increase of Ca^{2+} localised in the invasion area (Tran Van Nhieu *et al.,* 2013), and global responses, that spread in the whole invaded cell. The local versus global character of the responses plays a crucial role in the cytotoxicity of the bacteria, as a high and sustained Ca^{2+} elevation could lead to cellular death and limit the dissemination of the bacteria. Preliminary work was carried out by Tran Van Nhieu *et al.* (2013) and Sun, *et al* (2017) in order to analise the atypical Ca^{2+} responses induced by *Shigella* using modeling tools. Nevertheless, the models that have been proposed don't take into account the Ca^{2+} coming from the extracellular space, which has been demonstrated to have a crucial contribution to the Ca^{2+} responses. Thus, in this work we present a partial differential equation (PDE) model that takes into account extracellular Ca^{2+} entry through Plasma Membrane Channels, as well as Ca^{2+} and $InsP_3$ diffusion through the cytosol and the conditions caused by *Shigella*, in order to analise the global vs local character of the cytosolic [Ca^{2+}] responses during bacterial invasion. Numerical simulations show the impact of the plasma membrane channels in the local/global character of the [Ca^{2+}] responses, which implies that controlling extracellular Ca^{2+} entry to the cytosol could be crucial in order to find a mechanism to limit the dissemination of the bacteria.

Keywords: Calcium signalling, mathematical modelling, transport phenomena, *Shigella*, Store-Operated Calcium Entry

Disclosure of Interest: None Declared

Stochastic analysis of a minimal model of indirect negative self-regulation.

Guilherme Araujo[*1], Leonardo Maia[1]
[1]Instituto de Física de São Carlos, Universidade de São Paulo, São Carlos, Brazil

Your abstract : Genetic expression and regulation are intrinsically stochastic processes. Due to low molecular counts and random chemical reactions, intrinsic noise is a major feature to be controlled or explored by gene network designs. In this work, we develop an analytic modeling of a minimal network of negative feedback through the stochastic approach of the chemical master equation for the probability density of protein levels. The model highlights differences between direct and indirect self-regulation. We expand the nonlinear equations using Van Kampen's system size expansion and make connections to the deterministic limit. We find a steady-state noise control profile for the indirect feedback strength, and we can see an optimum feedback strength value for noise control in our model. We also analyze the model in the case of a Hill-type feedback function, making it a stochastic version of the Goodwin oscillator model.

Disclosure of Interest: None Declared

A model for iron regulation in animal cells

Alexandre Rocca[1], Nicolas Mobilia[1], Alexandre Donzé[2], Pascal Mossuz[3, 4], Jean-Marc Moulis[5, 6], Eric Fanchon[* 7]

[1]Univ. Grenoble Alpes, CNRS UMR 5525, TIMC-IMAG, F-38041, Grenoble, [2]Decyphir SAS, Decyphir SAS, Moirans, [3]CNRS UMR 5309, Inserm U1209, Université Grenoble Alpes , Institute for Advanced Biosciences, Grenoble 38700, [4]Institut de Biologie et Pathologie, CHU Albert Michallon, [5]Univ. Grenoble Alpes, Laboratory of Fundamental and Applied Bioenergetics (LBFA), Inserm, U1055 and Environmental and Systems Biology (BEeSy), Grenoble, [6]Bioscience and Biotechnology Institute (BIG), CEA-Grenoble, 17 ave des Martyrs, 38054 Grenoble Cedex 9, [7]TIMC-IMAG, CNRS & Univ Grenoble Alpes, Grenoble, France

Your abstract : Iron excess and deficiency underlie a range of pathological conditions in animals. Accordingly, regulatory systems maintain the proper iron amount to fulfill the needs of the whole body and of each individual cell, while avoiding deleterious effects. The latter may be due to lack of iron availability, e.g. at the active site of iron enzymes, or to reductive catalysis promoted by uncontrolled ferrous ions leading to the formation of reactive species such as the hydroxyl radical. Two major regulators maintain metazoan iron homeostasis, a systemic one relying on the circulating hormone hepcidin, and a ubiquitous cellular one organized around the Iron Regulatory Proteins.

We built a new mathematical model of cellular iron regulation in animal cells implementing the Iron Regulatory Protein (IRP), the iron storage protein Ferritin, and the import and export proteins Ferroportin and Transferrin receptor, respectively. An experimental scenario involving first iron scavenging and then iron replenishment via transferrin was applied to a panel of human cells. The results provided contraints for modeling. The uncertainty in some experimental parameters was dealt with by defining a region of parameter space rather than a unique instantiation, and consequently we reasoned on sets of models satisfying the constraints deduced from experimental data instead of a single optimal solution. Application of the modeling effort includes the identification of the main biological parameters that favor proliferation of leukemic clones detrimental to maturation, in acute myeloid leukemia for instance.

The authors acknowledge the support of the *Plan Cancer* through its Systems Biology program.

Disclosure of Interest: None Declared

A logical modeling approach to prepare and accelerate the design of ODE models. Application to the bile acids metabolism.

Lara Brueziere[*1], Arnaud Poret[2], Eliott Tixier[1], Claudio Monteiro Sousa[1], Jean-Pierre Boissel[1]
[1]NOVADISCOVERY, Lyon, [2]Laboratoire des Sciences du Numérique de Nantes, Nantes, France

Secondary topic : Methodological developments for Systems Biology

Your abstract : Developing a mechanistic disease model based on Ordinary Differential Equations (ODEs) may prove time-consuming when studying complex biological systems such as the human bile acids metabolism. Additionally, kinetic parameters of biochemical equations are rarely available in the literature.

To address these issues, we propose an approach based on an approximation of such a model using a Fuzzy Logic Graph (FLG) which is a Boolean model enriched with fuzzy logic operators. FLG models are considerably faster to develop, implement and simulate than more sophisticated models while still capable of qualitatively reproducing complex systems dynamics.

This first step facilitates the identification of key reactions and sub-mechanisms before incorporating them in a high-fidelity model. The reduction of the number of reactions (and therefore unknowns) generally leads to models that are computationally less demanding and that are more easily identifiable.

We present an application of the proposed methodology to a practical case study of the human bile acids metabolism. The biological context is described and different realistic perturbation scenarios are considered to highlight the auto-regulation mechanisms of the system. The FLG model is presented and the simulation protocol and outputs are discussed. Finally, the FLG model outputs are qualitatively compared to mechanistic ODE model simulations.

Disclosure of Interest: None Declared

A theoretical approach to understand the role of the retention mechanism in the rejuvenation process

Barbara Schnitzer[*1], Johannes Borgqvist[1], Niek Welkenhuysen[1], Marija Cvijovic[1]
[1]GÖTEBORGS UNIVERSITET, Göteborg, Sweden

Secondary topic : Methodological developments for Systems Biology

Your abstract : During yeast cell division damaged proteins are inherited asymmetrically such that most are retained within the mother cell, resulting in an ageing mother and a daughter cell with full replicative potential. However, daughters of old mothers are born with increasing levels of damage resulting in lower replicative potential. Remarkably, these prematurely old daughters can nevertheless give rise to rejuvenated cells with low damage levels and full replicative potential. The mechanisms of how aged cells give rise to young progeny are however not completely understood. We have developed a computational framework to elucidate the role of damage retention in the rejuvenation process, on both a single cell and population level. We further implement two distinct damage retention strategies: throughout the life of the mother cell its ability to retain damage is either constant or decreases with each division, referred to as static or dynamic retention. The proposed model is capable of simulating the complete cell lineage for both retention strategies and can explicitly track mother-daughter relations in dynamically growing yeast population accounting for the individuality of the cells.

Our approach suggests that a dynamic damage retention mechanism is favorable for asymmetrically dividing organisms, such as *S. cerevisiae*, as they lead to more resilient populations less prone to environmental stress and parameter variations. Further, by analyzing the full pedigree tree, more detailed information about the damage distribution between generations and siblings will be gained, allowing us to extract parameters and conditions that would lead to rejuvenation. With large-scale explorations of the properties of the whole population and following individual cells in this setting, we hope to shed light upon rejuvenation as an effect of damage retention in yeast.

Disclosure of Interest: None Declared

Multi-omics – MULT

Adaptive laboratory evolution generates a fast-growing Chlamydomonas mutant that accumulates lipids

Amphun Chaiboonchoe[*1], Bushra Dohai[1], David Nelson[2], Weiqi Fu[1], Basel Khraiwesh[2], Amnah Alzahmi[1], Dina Al-Khairy[1], Alexandra Mystikou[2], Ashish Jaiswal[1], Sarah Daakour[2], Mehar Sultana[2], Kourosh Salehi-Ashtiani[3]

[1]Science and Math, Laboratory of Algal, Systems, and Synthetic Biology, New York University Abu Dhabi, [2]Science and Math, Center for Genomics and Systems Biology (CGSB), New York University Abu Dhabi, [3]Science and Math, Laboratory of Algal, Systems, and Synthetic Biology and Center for Genomics and Systems Biology (CGSB), New York University Abu Dhabi, Abu Dhabi, United Arab Emirates

Secondary topic : Evolutionary and Ecological Systems Biology

Your abstract : Nitrogen and other nutrient depravations are known to induce lipid accumulation in *Chlamydomonas reinhardtii* and other microalgal species; however, such deprivations are generally accompanied by a reduction in growth rate, limiting productivity. In order to explore if there are alternative metabolic restructurings that can result in lipid accumulation without growth retardation, we carried out four rounds of UV mutagenesis and FACS selection to isolate mutants with increased lipid contents. One of the isolated mutants, herein referred to as CC-5163 mt+, was found to grow as fast as its parental CC-503 strain, while accumulating 3~5 fold higher neutral lipids. Whole genome sequencing performed on CC-5163 mt+, revealed 45 'high-impact' mutations with potential roles in lipid-related metabolic pathways. Specifically, mutations in a phosphofructokinase, a guanylate cyclase, a lipase, and a ferredoxin were discovered. RNAseq analyses of the mutant strain identified a large number of differentially expressed genes distinct from those involved in response to nitrogen starvation. Furthermore, the transcriptomic analysis revealed upregulation of key genes involved in lipid metabolism and. Additionally, strain- and state-specific metabolic models were generated for the mutant and the parental strain through integrating transcriptomic data with a genome-scale model of Chlamydomonas metabolism, *i*BD1106. Flux balance analyses (FBA) indicated higher fluxes through malate dehydrogenase, glutamate synthase (NADH), glutamate-ammonia ligase, and glutamate dehydrogenase in the mutant's chloroplast. Moreover, FBA revealed an increase of flux in mitochondrial TCA, a higher pyruvate production, and more permeation of citrate from the cytosol, implying that rerouting of carbon and energy flow within and from the mitochondria are key factors that have resulted in increased lipid accumulation in the mutant without compromising its growth rate.

Disclosure of Interest: None Declared

Cellular heterogeneity and stochasticity in normal and tumorous tissues

Clémentine Decamps[*1], Daniel Jost[1], Magali Richard[1]
[1]TIMC-IMAG, La Tronche, France

Secondary topic : Methodological developments for Systems Biology

Your abstract : In cancer, each tumor is unique and composed of cells with different identities and origins. This intra-tumor heterogeneity is a key player in cancer. In particular, the failures in cancer treatments are often associated to a wide heterogeneity in the cancer composition across patient populations. However, researchers are still at the very beginning of understanding which aspects of intra-tumor heterogeneity are relevant to cancer evolution and clinical studies. In particular, the contribution of tumour genome mutation, epigenome variation and tumour microenvironment remains largely understudied.

In this project, we propose to develop new methods to characterize the heterogeneity at two different levels: the variability between cell types and the variability internal to each cell type. First, we will develop signal processing algorithms to obtain tumor's composition and the specific characteristics of each cell type. Second, we will use statistical physics methods to quantify the epigenetic stochasticity in one tumor. Finally, we will use quantitative genetic models to understand how the intra-tumour heterogeneity is regulated and what are its physiological and pathological effects.

The resulting outcomes are expected to (i) bring significant methodological contributions to the analysis of cancer biological data, (ii) contribute to a better understanding of cell heterogeneity within complex tissue and (iii) open new therapeutic aspects to explore in medical research.

Disclosure of Interest: None Declared

Charting the cross-functional map between transcriptional regulators and cancer cell metabolism

Karin Ortmayr[*1], Sébastien Dubuis[1], Mattia Zampieri[1]
[1]INSTITUTE OF MOLECULAR SYSTEMS BIOLOGY, ETH ZURICH, Zurich, Switzerland

Secondary topic : Modelling Networks and Circuits

Your abstract :

Aberrant regulation of transcription factors (TFs) can trigger extensive reprogramming of cell metabolism that is associated with many human diseases, including cancer. However, a systematic approach to study the role of transcriptional regulators in mediating cancer metabolic rewiring is to date missing. To this end, we developed a new combined experimental-computational framework for (1) high-throughput metabolic profiling of 54 adherent cancer cell lines and (2) the integration of metabolic profiles with previously published transcriptomics and proteomics datasets. By charting a genome-scale map of TF-metabolite associations in human, we unravel a large space of dependencies between TFs and metabolic pathways. We demonstrate that these TF-metabolite associations can serve as a powerful tool for predicting TFs responsible for metabolic changes observed in vivo in patient-derived tissue samples, and recover drivers of oncogenic transformation from patient metabolic profiles in renal, lung and colon cancer cohorts. To resolve the flow of signaling that can contribute to altering TF activity, we establish an in silico framework to chart a blueprint interaction map between TFs, metabolites and kinases. This new map can serve as a unique resource for generating hypotheses and designing target-oriented experimental approaches for in-depth mechanistic studies identifying metabolic regulators of transcriptional reprogramming. Overall, this new systematic platform for charting genome-scale functional associations between metabolites and TFs in human cells can introduce a new paradigm in the analysis of patient-derived metabolic profiles and the development of dedicated intervention strategies to counteract reprogramming of cellular metabolism in cancer.

Disclosure of Interest: None Declared

Toward a computational multi-omics integrative framework for systems toxicology

Alain Sewer* [1], Björn Titz[1], Blaine Phillips[2], Justyna Szostak[1], Catherine Nury[1], Thomas Schneider[1], Ashraf Elamin[1], Emmanuel Guedj[1], Ee Tsin Wong[2], Marja Talikka[1], Brian Keppler[3], Nikolai Ivanov[1], Patrick Vanscheeuwijck[1], Florian Martin[1], Manuel Peitsch[1], Julia Hoeng[1]
[1]PMI R&D, Philip Morris Products S.A., Neuchâtel, Switzerland, [2]Philip Morris International Research Laboratories Pte. Ltd. , Singapore, Singapore, [3]Metabolon Inc., NC 27709, United States

Secondary topic : Multi-omics

Your abstract :

Background: "Systems Toxicology" refers to the application of Systems Biology to toxicological risk assessment. We recently developed a network-based approach to comparatively quantify the biological impacts of exposures to complex mixtures. In this approach, input transcriptomics data are evaluated in the context of relevant biological networks consisting of assembled molecular signaling pathways. Here, we take the first steps in developing an integrative Systems Toxicology framework for complementary data modalities, such as proteomics, metabolomics, and miRNAomics, to set up a genuine multi-omics biological impact quantification pipeline for toxicity assessment.

Methods: To establish and test data integration approaches, we leveraged recently generated multi-omics data from a mouse inhalation toxicology study, including sample-matched mRNA, miRNA, protein, and metabolite profiles for up to 144 samples. Building on our previous work, we proceeded in a two-step approach. First, we extracted the relevant biological mechanisms impacted by the exposure and constructed their representations across the various data modalities, testing several combinations of data-driven and prior knowledge-driven approaches to achieve an augmented mechanistic interpretation. Second, we re-evaluated these mechanistic findings in the biological impact assessment context to draw conclusions about the relative impact of the tested exposures.

Results: We established a multi-omics data processing pipeline in the R computational environment using relevant packages, such as Multi-Omics Factor Analysis (MOFA) and mixOmics. Multivariate methods capturing common variations across data modalities and exposures are used as well as enhanced overrepresentation analyses providing biological contexts to the resulting abstract data structures. We included metabolic pathways to complement the prior knowledge and deduce novel inter-modality relationships. To assess perturbation impact, we adapted the competitive and self-contained enrichment statistics used in transcriptomics. In the context of the considered experimental dataset, we identified latent factors capturing treatment responses and explored in more detail several relevant mechanisms, such as inflammation and oxidative stress.

Conclusions: Computational approaches, such as MOFA, are very pertinent to Systems Toxicology, as they aim to disentangle molecular variation into distinct components, thereby reinforcing the toxicological insights.

Disclosure of Interest: None Declared

Gene-specific correlation analysis of mRNA and protein levels in colorectal cancer cell lines

Fatemeh Zamanzad Ghavidel[* 1], Inge Jonassen[1], Alvis Brazma[2], Jyoti S. Choudhary[3]
[1]Department of Informatics, University of Bergen, Bergen, Norway, [2]European Bioinformatics Institute (EMBL-EBI), Wellcome Trust Genome Campus, Hinxton, Cambridge, United Kingdom, [3]Institute of Cancer Research, London, United Kingdom

Secondary topic : Multi-omics

Your abstract : The central dogma of molecular biology includes translation of genetic information from mRNA to protein. Quantitative analyses of the correlation between the abundance of mRNAs and corresponding proteins can be weak and some times moderate. The level of correlation varies between experimental conditions assessed and also between organisms. Several biological factors, e.g., post-translational regulation and modifications have been shown to influence the correlation.

In this work, we performed a correlation analysis to look for possible correlation between gene and protein expression in cancer cell lines. We performed a comprehensive correlation study of protein expression profiles (7000 proteins measured) of 50 colorectal cancer cell lines and the corresponding gene expression levels from two public data bases: Cancer Cell Line Encyclopedia (CCLE) and Sanger Genomics of Drug Sensitivity in Cancer Project (GDSC). We identified genes with discordance/concordant gene and protein expression levels. This information has important implication for diagnosis and therapeutic targets. Moreover, gene-protein specific correlation indicates a GO- dependent concordance of protein/mRNA expression. We found out moderate cell line–specific correlation (median Spearman's r = 0.59). Highly variable mRNAs tend to correspond to highly variable proteins (Spearman's r = 0.68), although with a wide distribution. Notably, several genes, including *TP53*, displayed high variation at the protein level despite low variation at the mRNA level, implicating significant post-transcriptional modulation of their abundance.

Disclosure of Interest: None Declared

Unraveling transcriptional regulation of starch metabolic genes in cassava through computational prediction with yeast-one hybrid validation

Saowalak Kalapanulak[*] [1, 2], Nattawet Sriwichai[2], Treenut Saithong[1, 2], Malinee Suksangpanomrung[3], Supatcharee Netrphan[3]

[1]Bioinformatics and Systems Biology Program, School of Bioresources and Technology, King Mongkut's University of Technology Thonburi, [2]Systems Biology and Bioinformatics Research Group, Pilot Plant Development and Training Institute, King Mongkut's University of Technology Thonburi, Bangkok, [3]National Center for Genetic Engineering and Biotechnology (BIOTEC), National Science and Technology Development Agency (NSTDA), PathumThani, Thailand

Secondary topic : Multiscale Systems Biology

Your abstract : While the significance of cassava, one of the most important economic starchy root crops of the world, keeps increasing, the understanding on the transcriptional regulation of the starch metabolism in cassava is very limited. To gain insight into the transcriptional regulation of starch metabolic genes in cassava, systems biology approach was applied to reconstruct a high-quality transcriptional regulatory network (TRN) of starch metabolic genes. The integrative approach including reversed engineering method using several gene expression datasets of Arabidopsis and cassava and cis-acting regulatory elements analysis was applied for inferring high-confidence TRN. The proposed TRN of cassava consisted of 194 interactions between 68 starch metabolic genes functioning in carbon dioxide fixation, sucrose synthesis and starch synthesis process and 101 transcription factors (TFs). Genes encoding for ADP-glucose pyrophosphorylase (AGPase) were selected for validation using yeast-one-hybrid for confirming the binding affinity between the proposed TFs and their promoters of the target genes in Thai cassava cultivar (KU50). Firstly, all eight AGPase genes including three genes encoding for small subunit (i.e., *APS1-1, APS1-2* and *APS2*) and five genes encoding for large subunit (i.e., *APL1-1, APL1-2, APL2-1, APL2-2* and *APL3*) were identified via comparative genomics approach in cassava AM560 genome. Five of them (i.e., *APS1-1, APS2-1, APL1-1, APL2-1 and APL3*) have been cloned their promoters from the storage root tissue of Thai cassava cultivar (KU50). From our reconstructed TRN, the six TF genes (i.e., *cassava4.1_007456m.g, cassava4.1_013116m.g, cassava4.1_020656m.g, cassava4.1_011038m.g, cassava4.1_014818m.g, cassava4.1_015610m.g*) and the other seven TF genes (i.e., *cassava4.1_014818m.g, cassava4.1_015610m.g, cassava4.1_007456m.g, cassava4.1_013116m.g, cassava4.1_020656m.g, cassava4.1_012631m.g, cassava4.1_015705m.g*) have been proposed to control *APS1-1* gene and *APL3* gene, respectively. After performing yeast-one-hybrid validation, three from six proposed TF genes controlling *APS1-1* gene and four from seven proposed TF genes controlling *APL3* gene demonstrated the positive results. Finally, up to 57% of accuracy was achieved in this work. These may demonstrate the contribution of computational prediction for reducing time in crop breeding program using molecular targeted approach in the near future.

Disclosure of Interest: None Declared

Integrative network analysis of time course microRNA and mRNA data using multiple tools

Krutik Patel[* 1] and Shanley Group, Newcastle University.
[1]Institute for Cell & Molecular Bio Sciences, NEWCASTLE UNIVERSITY, Newcastle, United Kingdom

Secondary topic : Multiscale Systems Biology

Your abstract : Three key challenges in systems biology are: big data analysis, time course analysis and multi 'omic integration. Here I address these challenges by using mutliple bioinformatic tools on time course chondrogenesis mRNA and miRNA data from Barter et al (2015). This generated three types of inputs for network visualisation: time course differential expression analysis, pathway enrichment analysis and mRNA-miRNA correlation analysis. In the first step, the mRNA and miRNA datasets are put through time course differential expression analysis using limma. Only genes with an adjusted P.value < 0.05 were kept for network visualisation. Next, the bioconductor package anamiR is used to integrate the normalised mRNA and miRNA data sets to find enriched pathways. From anamiR we get a ranked list of enriched KEGG and reactome pathways. A further bioconductor package mirIntegrator, was used to integrate the mRNA and miRNA data by log2FC. mirIntegrator reveals which pathways were enriched at each time point. Using both tools we identified which KEGG/ reactome pathways to investigate during network visualisation. Lastly, the R package mircomb was used to find the correlations between every possible mRNA-miRNA interaction. Mircomb identified interactions found in up to four predictive target databases: microCosm, miRDB, targetscans and miRSVR. Under the assumptions that miRNAs and their respective mRNA targets should negatively correlate and that predictive databases are largely correct, the mircomb results was filtered for correlations < -0.3 and mRNA-miRNA interactions should be present in at least two database. The outcome is three inputs for data visualisation. Cytoscape and pathviso are used to load wikipathway networks which the pathway enrichment analysis showed are significant e.g. PI3K-Akt signalling pathway. Then I annotate these pathways with mRNA-miRNA interactions that have negative correlation and occur in at least two database from the mRNA-miRNA correlation analysis. Finally, I use the log2FC time course differential expression analysis to visualise the differences that occur in the miRNA integrated pathways at different time points. Overall, we have constructed a method of finding potential mRNA-miRNA interactions that occur in large time course datasets to inform further laboratory investigation and ultimately for building mathematical models.

Disclosure of Interest: None Declared

Systematic identification of flux regulation through enzyme phosphorylation

Brendan Ryback[*1] on behalf of Sauer, Zrinka Raguz[1], Peng Xue[1], Ruedi Aebersold[1], Uwe Sauer[1]
[1]Biology, ETH ZURICH, Zurich, Switzerland

Secondary topic : Quantitative Systems Physiology

Your abstract : Post-translational protein modification is an evolutionarily conserved mechanism that enables rapid cellular adjustment and maintenance of homeostasis. Recent advances in phospho-proteomics technology have enabled the identification of thousands of novel phosphorylation sites in the *Saccharomyces cerevisiae* proteome. However, elucidating the biological function of a given phosphorylation event depends on the integration of additional physiological information not contained in the phospho-proteome. Thus, the vast majority of identified phosphorylation sites remain without an ascribed biological function.
Here we applied a systematic approach to generate hypotheses on the functional role of phosphorylation sites for the subset of proteins related to metabolism. We designed 18 different growth media encompassing combinations of carbon, nitrogen, and sulfur sources as well as chemical and physical stressors. For each condition we quantified physiological rates during exponential growth, steady-state intracellular metabolite concentrations as well as protein and phospho-protein abundances using SWATH-MS. We observed doubling times spanning two to seven hours, diverse exchange rates for 12 nutrients and secretion products, and a variety of abundances for approximately 400 intracellular metabolites. We quantified the abundances of over 3700 proteins (including 600 metabolic enzymes) and 1500 phosphopeptides. Analysis of the protein and metabolite data revealed low variability between biological replicates and hierarchical clusters of conditions consistent with prior expectations.
We use the physiology data to constrain a genome-scale metabolic model to estimate the steady-state metabolic fluxes. Correlations between these fluxes and the relative phospho-peptide abundances detected in the corresponding enzymes across conditions allow us to rank phospho-sites by their probability to exert regulatory roles in metabolism. These will serve as candidates for targeted mutagenesis experiments elucidating the interactions between signaling and metabolic networks in regulating cellular homeostasis.

Disclosure of Interest: None Declared

Profiling individual plants to probe plant stress responses and their interaction under field conditions

Daniel Cruz[* 1], Sam de Meyer[1], Joke Ampe[1], Heike Sprenger[1], Tom Van Hautegem[1], Steven Maere[1]
[1]Plant Systems Biology, VIB UGENT, Ghent, Belgium

Your abstract : Climate change and the growing world population are posing increasing pressure on our food supply. The limited area available for agriculture urges us to develop crops with higher yields and improved stress tolerance. *Zea mays* is among the most important crops for both human food and livestock feed production. Improvements in the yield potential and stress tolerance of maize would thus have a considerable impact on food safety. So far, the molecular effects of environmental factors or stress responses on plant phenotypes are mostly investigated in a tightly controlled setup in the lab or greenhouse, usually by disturbing one environmental parameter at the time. The results of such studies often do not translate well to an agricultural setting where plants are exposed to several kinds of environmental stresses acting in concert. We developed a new experimental setup to study plant stress responses and their phenotypic consequences in a natural field setting, involving profiling of the transcriptome, metabolome and phenotypes of individual field-grown maize plants of the same inbred line, thereby focusing only on the molecular and phenotypic effects of natural micro-environmental variation. We showed that the subtle uncontrolled combinations of environmental perturbations that occur in this setup yield valuable information on the molecular wiring of maize stress response pathways under field conditions. Furthermore, we showed that the individual plant data generated in our experimental setup can be used to train machine learning models predicting plant phenotypes as a function of the plants' transcript and metabolite profiles, thereby identifying new candidate genes for maize yield traits. Additionally, these profiles were used to generate gene regulatory networks which allowed to make new functional predictions. Finally, we proposed methodologies to determine spatial effects in the field that affect gene expression with certain patterns. Because the data is generated directly in the field, we expect that our experimental design should more easily translate to agricultural applications.

Disclosure of Interest: None Declared

Temporal omics data integration using functional data analysis. Application to radiation-induced transcriptomic and proteomic time-course expressions.

Mohamed Amine Benadjaoud[* 1], Valérie Buard[2], Georges Tarlet[2], Agnès François[2], Philippe Chan[3], David Vaudry[3], Fabien Milliat[2], Olivier Guipaud[2]

[1]PSE-SANTE, SERAMED, [2]PSE-SANTE, SERAMED/LRMed, THE NATIONAL INSTITUTE FOR RADIOLOGICAL PROTECTION AND NUCLEAR SAFETY (IRSN), Fontenay aux roses, [3]PISSARO Proteomic Platform, Institute for Research and Innovation in Biomedicine, University of Rouen, Mont-Saint-Aignan, France

Secondary topic : Methodological developments for Systems Biology

Your abstract : The molecular components of biological systems across multiple conditions can be assessed through various technologies which simultaneously collect a large set of a specific omic data (gene expression, protein abundances, ...etc). Therefore, these different layers have to be analyzed and integrated in order to provide a more comprehensive view of temporal biological processes.

Such analyses are challenging for several reasons: high-dimensionality, missing values, sparse time sampling, temporal correlation, noise…etc. An additional issue with time course data consists on inter omics timing differences. Ignoring these delays can remain hidden some crucial properties of activation and regulation in the process of interest.

Functional data analysis (FDA) is a statistical technique that treats the time-course measurements as a discretization on an underlying smooth process. This allows: the inclusion of non-uniformly sampled data, enables to estimate expression at non measured times, the imputation of missing values and the removal of noise via penalization. In this framework, the time warping is often used as a preliminary step in FDA to reduce phase variation and often appears as an intermediate step followed by a specific treatment of the synchronized functions.

In this study, a special attention is being given to the warping functions to achieve an integration analysis in presence of two types of omic data type designed by Omics-A and Omics-B: firstly, each curve the omics-A sample serves as template for all Omics-B curves in a pairwise synchronization procedure. The resulting warping function estimates are then scored using a functional principal component analysis in order to isolate the B-Omics linked to the template curve in a granger causality sense. Finally, an appropriate thresholding of the distances after the pairwise synchronization step allows a clustering of mixed Omics-A and Omics-B sharing a common underlying pattern with a Granger-causality interpretation.

Simulations demonstrate that the proposed method compares well with other existing similarity or time-delayed correlation methods where the continuous biological processes still discretized and restricted to the observed time points. The proposed method is illustrated in the integration of temporal transcriptomic and proteomic fold-changes of human primary endothelial cells (HUVECs) exposed to a high radiotherapy dose fraction (20 Gy) measured from 12 hours to 3 weeks post-irradiation.

Disclosure of Interest: None Declared

A two-step modelling approach to predict drug sensitivity in human cancer cell lines

Nina Kusch[*1], Andreas Schuppert[1]
[1]JRC COMBINE, RWTH AACHEN UNIVERSITY, Aachen, Germany

Your abstract : Cancer continues to present a virtually unparalleled challenge to modern health care due to its inherent heterogeneity and complexity which exacerbate efforts to identify the causes and regulatory factors driving disease progression and clinical outcome. Since cell lines constitute a valuable tool in cancer research, a number of large-scale data sets of human cancer cell lines have been produced and published, featuring increasingly multi-omics characterizations of cells in combination with response profiles to a range of anti-cancer drugs.
While well-established driving factors for cancer have been identified in diverse data types such as gene expression and somatic mutations, there is no universally accepted straight-forward strategy to integrate features from different data types and scales into one joint model as of yet. In order to utilize the potentially complementary information hidden in different omics data in equal measure, we propose a two-tiered approach to model drug sensitivity in cancer cell lines based on both global patterns of gene expression and selected mutation profiles. By separately identifying drug-specific sub-models based on exactly one type of omics data each in a first step before merging them into one final model in a second step, we aim to counteract the issues arising from the integration of diverse predictor variables from multi-omics data into one classification model.

Disclosure of Interest: None Declared

Heat adaptation in pigs: phenotypes, genotypes, blood transcriptomics and metabolomics

Guillaume Devailly[*] [1] and PigHeat
[1]GenPhySE, INRA, Castanet Tolosan, France

Your abstract : Heat adaptation in pigs: phenotypes, genotypes, blood transcriptomics and metabolomics

Guillaume Devailly, Yann Labrune, Katia Feve, Laure Gress, Jean-Luc Gourdine, Hélène Gilbert, David Renaudeau, Juliette Riquet

Heat wave frequency is increasing due to global warming, resulting in consequential impacts on agricultural productions. In temperate production pigs, heat waves reduce production performances and cause animal discomforts. Improving heat resistance in pigs is therefore needed to mitigate the effects of the global warming.
Caribbean Creole pigs are well adapted to tropical climate, but show low production values, the exact opposite of Large White pigs. Animals from a back-cross of Large White pigs with Creole pigs where raised in experimental units of INRA in both tropical and temperate climate. Animals in temperate climate where further challenged with a two weeks artificial heat wave. Animals production traits and thermo-regulatory responses where recorded and associated with their genotypes. Blood samples of a subset of animals where used for metabolomics and transcriptomics analyses in both environments, and throughout the induced heat stress (N=180 per conditions).
This dataset was used to identify variants, transcripts and metabolites associated with heat resistance. We further investigated the genetic control of transcript (eQTL) and metabolite (metaboQTL) abundance. Altogether, our results paves the way of a better selection route for heat resistance in pigs.

Disclosure of Interest: None Declared

Integrated statistical model based on transcriptome and metabolome in the biophylaxis metabolism of Angelica actiloba

Masamitsu Harada[* 1], Naoaki Ono[1, 2], Huang Ming[1], Md Altaf-Ul-Amin[1], Shigehiko Kanaya[1, 2], Ken Tanaka[3]

[1]Graduate School of Science and Technology, [2]Data Science Center, NARA INSTITUTE OF SCIENCE AND TECHNOLOGY, Ikoma, [3]College of Pharmaceutical Science, Ritsumeikan University, Kusatsu, Japan

Your abstract : The root of *Angelica acutiloba* is one of the popular ingredients used in the Kampo medicines or traditional Chinese medicines. They have various of benefits and efficacy such that alleviation suppression of women's disease, analgesic effect, anti-inflammatory effect, vasodilator action and so on. It is worth noting that the active element of *A. acutiloba* is also involved in biophylaxis. Recently it is reported that when vermines such as swallowtail butterflies attacks *A. acutiloba*, it increases production of β-caryophyllene to attract some bee which is natural enemy of the butterflies. β-caryophyllene shows anti-inflammatory effect for human and also other medicinal compounds will increase with them. In the present study, we investigated the biosynthesis pathways related with production β-caryophyllene and other secondary metabolites in *A. acutiloba* on the defensive reaction against herbivorous insects. We measured both metabolome and transcriptome of *A. acutiloba* after the exposure of the elicitors (0h, 6h, and 12h) to understand molecular mechanism of the defensive metabolic reactions. The results showed that 14 compounds out of 23 metabolites and 5,418 genes out of 93,573 transcriptomics have significantly changed after the exposure. Differentially expressed genes were detected from transcriptome and mapped for metabolic pathways, steroid biosynthesis pathways and Sesquiterpenoid biosynthesis pathways were detected by enrichment analysis. We also found that the Mevalonate pathway, which is associated with biosynthetic pathway of terpenoid compounds such as ligustilide, β-caryophyllene and terpinene was also activated. Furthermore, we are constructing a statistic model based on tBayesian network to evaluate the metabolic changes in pathway in detail referred to the knowledge-based database KEGG database by using both metabolome and transcriptome data. Because individual analysis of multi-omics often leads to inconsistent result, our approach integrates both metabolite and gene expression data based on a unified framework based on the Bayesian network model to evaluate the changes in the metabolic systems statistically.

Disclosure of Interest: None Declared

A systemic change of fatty acid metabolism regulation in Atlantic salmon after CRISPR/Cas9-mediated knockout of elovl2, Δ5-fads and Δ6-fads genes

Yang Jin[*1], Alex K. Datsomor[2], Jon Olav Vik[3], Keshuai Li[4], Rolf Erik Olsen[2], Rolf B. Edvardsen[5], Anna Wargelius[5], Per Winge[2], Fabian Grammes[1]

[1]Biosciences , Norwegian University of Life Science, Ås, [2]Biology, Norwegian University of Science and Technology, Trondheim, [3]Chemistry, Biotechnology and Food Science, Norwegian University of Life Science, Ås, [4]BioMar Group, Trondheim, [5]Institute of Marine Research, Bergen, Norway

Secondary topic : Systems Biology for Synthetic Biology

Your abstract : Atlantic salmon can synthesise long chain polyunsaturated fatty acids (LC-PUFA) via fatty acid elongases (elovls) and desaturases (fads). The pathway of LC-PUFA synthesis has been addressed for decades in salmon, but the regulation of *elovls* and *fads* genes especially their interaction with other genes in lipid metabolism pathways needs to be further investigated. Here, we used CRISPR/Cas9 technology to generate three genetic modified strains of salmon by knocking out 1) *elovl2* gene, 2) all *fads* genes (*Δ5-fads*, *Δ6-fadsa*, *Δ6-fadsb* and *Δ6-fadsc*), and 3) *Δ6-fadsb* and *Δ6-fadsc* genes. The knockout (KO) salmon was co-cultivated in with wildtype (WT), fed diets containing either high-PUFA or low-PUFA. Whole transcriptomic analysis has revealed 45 and 349 differentially expressed genes (DEGs, FDR <0.05) in liver of *elovl2*-KO and all-*fads*-KO salmon respectively compared to WT, suggesting a clean and efficient KO of targeted genes by using CRISPR technology. Most of the DEGs were involved in lipid metabolism pathways of salmon, which was likely due to expression change of other genes to compensate for reduced level of synthesised LC-PUFA in KO-salmon. On the other hand, ~3000 DEGs was identified in *Δ6-fadsb*/c-KO salmon compared to WT. This could due to off-targeted effects or other reasons, which needs to be further investigated.

A reduced transcription of *elovl2* gene was observed in *elovl2*-KO salmon, but *Δ5-fads*, *Δ6-fadsa* and *Δ6-fadsb* genes were elevated. This was likely correlated to increased *srebp1* transcription, as lipid genes containing SREBP motifs in their promoter region showed significant up-regulation in *elovl2*-KO. The efficiency of *elovl2*-KO was also investigated by incubating isolated hepatocytes with ^{14}C-18:3n-3, where we observed decreased level of the end product ^{14}C-22:6n3 in LC-PUFA synthesis pathway, but increased ^{14}C-20:5n3 and ^{14}C-22:5n3 which synthesised before the *elovl2*-controlled step. All-*fads*-KO and *Δ6-fadsb*/c-KO salmon both had decreased expression of *Δ5-fads*, *Δ6-fadsa* and *Δ6-fadsb* genes in liver, but the level of expression changes was much higher in all-*fads*-KO. The expression of *elovl2* and *elovl5* genes was not changed in both KO. The *srebp1* genes was only up-regulated in all-*fads*-KO salmon. Regardless of the KO-targets, the KO-induced expression changes of genes were similar between salmon fed low-PUFA and high-PUFA diets, but the level of changes on lipid gene expression was much higher when salmon fed low-PUFA diet.

Disclosure of Interest: None Declared

NEW TOOLS FOR INTEGRATIVE VIEW ON REGULATORY MECHANISMS INVOLVED IN INTERSPECIES MOLECULAR INTERACTIONS

Francesco Pezzini[1], Ekaterina Shelest[*1]
[1]Bioinformatics Unit, GERMAN CENTRE FOR INTERGATIVE BIODIVERSITY RESEARCH, Leipzig, Germany

Secondary topic : Methodological developments for Systems Biology

Your abstract : One of important mechanisms of interspecies interactions relies on secondary metabolites (SMs), structurally diverse natural products that allow organisms to invade, colonize, resist, and respond to each other's actions. To get a comprehensive picture of interspecies communication, we need to understand the mechanisms of SM regulation. Applying systems biology approach, we develop methods and tools to analyse and integrate processes going at different levels to see the bigger picture.

Since SM genes are typically silent under normal conditions, experimental detection of SMs remains a serious challenge for wetlab scientists. Therefore, computational methods for detection of SM genes are needed. To this end, we recently developed tools for SM genome mining (SMIPS) and for promoter-based prediction of SM gene clusters in eukaryotic genomes (CASSIS (*Bioinformatics, 2016; Nucleic acid res, 2017*)). But the next, more challenging question is how the clusters are brought to action. This is a multi-level process starting with triggered signalling pathways and transcription factors (TFs), but also involving regulation on epigenetic level including changes in nucleosome positioning, which are linked to accessibility of TF binding sites. The role of nucleosome positioning in SM regulation is less investigated than chromatin modifications; to address this problem, we developed a novel tool for nucleosome profiling and nucleosome pattern detection.

In the poster, we show how two our novel methods, CASSIS for SM cluster prediction and NEPtuner for nucleosome profiling and nucleosome pattern detection, are brought together in one workflow to investigate SM regulation in fungi. In brief, CASSIS detects SM clusters by looking for co-localised promoters with common motifs (potential TF binding sites). The NEPtuner core profiling function is integrated in a pipeline, which uses the profile for genome-wide identification of (i) well-phased nucleosome arrays and (ii) regular patterns in the promoter/TSS regions of genes (-1 nucleosome/NDR/+1 nucleosome).

After detection of the SM clusters, we analyse their expression status, link this information to the occurrence TF binding patterns and see if the motifs are accessible for the TFs. In this sense, we compare the behaviour of nucleosomes in active and silent clusters with the help of NEPtuner. We will show several examples of application of our methods to investigation of SM production upon fungal-bacterial interaction.

Disclosure of Interest: None Declared

Modeling transcription factor activity based on target gene expression

Janis Neumann[*1], Andreas Beyer[1]
[1]Cellular Networks and Systems Biology, CECAD, Cologne, Germany

Secondary topic : Methodological developments for Systems Biology

Your abstract : Transcription factors (TFs) bind to DNA to modulate the expression of their target genes. While the mechanisms of action have been extensively studied for many TFs, it remains hard to quantify their specific activity. The activity of a TF cannot directly be measured at high-throughput. It has been proposed to model the activity of TFs using the effects they have on the expression of their target genes. Existing strategies often linearly regress gene expression levels on the probability of each TF to control a given gene. Several variations of this concept have been developed. However, a systematic validation of the approach in general and individual methods in particular has not been carried out.

To this end, we have designed a framework that allows to assess the biological relevance and the performance of the different methods modeling the TF activity. At its core, it makes use of biological data in which a priori knowledge of the activity of a transcription factor exists – namely, TF knockdowns. We rank the methods based on their ability to identify the TF that was knocked down based on expression changes.

Expression data derived from mouse embryonic stem cells and a human lymphoblastoid cell line was exploited in this framework to assess the performance of both published and novel methods. These methods include different ways of determining TF targets, data processing approaches, and modeling methods. All possible combinations of methods were tested to both find optimal strategies and thoroughly investigate the performance of each method. This work revealed important differences in how well individual transcription factors can be modeled. Moreover, several strategies that improve upon previously published modeling methods could be identified.

Disclosure of Interest: None Declared

Modeling spatial genomic interactions with the Hawkes model

Anna Bonnet[* 1], Vincent Rivoirard[2], Franck Picard[1]
[1]LBBE, Université Lyon 1, Villeurbanne, [2]CEREMADE, Université Paris Dauphine, PARIS, France

Secondary topic : Methodological developments for Systems Biology

Your abstract : spatial localization of many DNA-protein interactions is now available thanks to the development of ChIP-Seq protocoles and their investigation calls for adapted statistical methods. Many methods were developped for peak calling, but few were proposed for the downstream analysis of peak-like data, whereas the spatial structure of such data may contain relevant biological information, like binding constraints for instance. Associations between the occurrences of two genomic features are usually assessed by overlaps, but here we propose a statistical model to precisely quantify the spatial interactions between the location of binding events. Our methodology relies on a multivariate spatial process, the Hawkes model, that can also be interpreted in terms of a graphical model to
highlight spatial dependencies between genomic features.
Using our method, we propose two applications : first, we explore the chromatin landscape of replication origins, and we highlight attractive and repulsive patterns that can be related to the regulation of the spatial program of replication. We then apply our method to study the co-localization between hotspots of recombination, transcription start sites (TSSs) and CpG islands (CGIs). We compete our method with both pairwise and multivariate approaches, implemented in the packages GenometriCorr and ppstat respectively. We highlight in particular the interest of performing a multivariate analysis, we show that our procedure describes with more details the complex patterns of spatial interactions and also provides estimates that are very convenient for interpretation.

Disclosure of Interest: None Declared

Data analysis automation and databases as key tools to multiple sources genomics data integration: starting from the legume model Medicago truncatula

Stefano Colella[*1], Ilana Lambert[1], Christine Paysant-Le Roux[2,3], Marc Tauzin[1], Cécile Guichard[2,3], Jean-Philippe Tamby[2,3], Marc Lepetit[1], Véronique Brunaud[2,3], Marie-Laure Martin Magniette[2,3,4]

[1]Laboratoire des Symbioses Tropicales et Méditerranéennes (LSTM), IRD, CIRAD, INRA, SupAgro, Univ Montpellier, Montpellier, [2]Institute of Plant Sciences Paris Saclay (IPS2), CNRS – INRA – Université Paris-Sud – Université Evry – Université Paris-Saclay, [3]Institute of Plant Sciences Paris Saclay (IPS2), Paris Diderot – Sorbonne Paris-Cité, Orsay, [4]UMR MIA-Paris, AgroParisTech – INRA – Université Paris-Saclay, Paris, France

Secondary topic : Methodological developments for Systems Biology

Your abstract : Genome sequencing paved the way to the beginning of big data science, a central resource for the development of systems biology. Microarrays and, more recently, Next Generation Sequencing (NGS) allow the study of global gene expression and of other molecular events (*e.g.* chromatin and histone modifications, DNA methylation) relevant to genome regulation in different biological processes. Despite the existence of large-scale coordinated genomics projects, like for example pENCODE [Lane AK, *et al.* Annu Rev Genet. 2014], single laboratories generate more and more independent datasets. Unfortunately, even if almost all data are stored in repositories, their organisation and format(s) are still a limiting factor to their use in meta-analysis. Databases have a recognized central role to move from integrative genomics to systems biology [Philippi S and Köhler J. Nat Rev Genet. 2006] and the standardisation of data analysis is key to perform realistic data comparisons. The GEM2Net database [Zaag R, *et al.* Nucleic Acids Res. 2014] for stress analysis in *Arabidopsis thaliana* is a collection of co-expression clusters, complemented with other information for enrichment analyses, to generate a better understanding of gene expression networks underlying different biological functions. We are planning the development of a novel GEM2Net-*plus* database for data generated for the legume model *Medicago truncatula*. This database will integrate RNAseq transcriptome data thanks to a standardized analysis pipeline we developed in R to automate the generation of co-expression clusters. The R pipeline includes tools tested and validated in methods comparative evaluation published studies. Our long-term plans include the extension of this database to other legumes to allow the comparison of gene expression networks in different species. Furthermore, using gene orthology information, researchers could use existing data to generate working hypothesis even when still lacking RNAseq experimental data on their species of interest. Both the pipeline and the database are in standard formats to allow easy transfer to other than legumes organisms. The combination of standardized analysis pipelines and *ad hoc* database tools is in our opinion a novel way to share data in a given scientific community. Such common automated strategy and repository will ease multiple datasets comparisons thus creating an opportunity to a full use of integrative genomics datasets in systems biology approaches.

Disclosure of Interest: None Declared

Multiscale Systems Biology – MULT

Towards a whole-cell model of Mycoplasma pneumoniae

Balazs Szigeti[* 1, 2], Arthur Goldberg[1, 2], Jonathan Karr[1, 2]
[1]Icahn Institute and Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, [2]Icahn Institute for Genomics and Multiscale Biology, New York, United States

Secondary topic : Methodological developments for Systems Biology

Your abstract : Whole-cell (WC) dynamical models that predict phenotype from genotype by accounting for every gene product and their interactions are needed to personalize medicine and rationally engineer microorganisms. Our long-term goal is to develop comprehensive and predictive WC models. Previously, we and others demonstrated the feasibility of WC models by reporting the first model which represents each characterized gene function of the bacterium *Mycoplasma genitalium*. We achieved the model through an ad hoc combination of data aggregation, rule-based modeling, model composition, multi-algorithmic simulation, and unit testing. However, the model mispredicts several phenotypes, the model does not represent several key pathways, and the model is difficult to expand and improve. Toward WC models that can drive bioengineering, we are piloting a more comprehensive model of *Mycoplasma pneumoniae*, a closely related and better-studied species. To enable more comprehensive models, we and others are also systemizing and scaling our approach by developing software for building, simulating, and analyzing WC models, including *Datanator* and *WC-KB* for aggregating and organizing data for WC modeling, *WC-Model-Gen* for programmatically designing models from large data, *WC-Lang* for describing composite models, *WC-Sim* for simulating multi-algorithmic models, and WC-Test for verifying models. Currently, the model represents the transcription, translation, and RNA and protein degradation of *M. pneumoniae,* with tunable granularity from the single-nucleotide to whole-molecule level. Going forward, we plan to use our new tools to broaden and deepen the model beyond the physiology and biochemistry represented by our *M. genitalium* model to represent additional processes such as the maintenance of the membrane potential, additional gene products such as small non-coding RNA and small proteins, and additional molecular mechanisms such as the sequestration of DnaA from replication initiation by YabA-DnaN. We expect the model will better predict the phenotypes of gene deletions, better explain cell cycle dynamics, and better account for energy usage than our *M. genitalium* model. We anticipate that the model will be the most comprehensive model of any organism to date, and that the model will help bioengineers build the first rationally-designed organisms. Availability: Open-source at https://github.com/KarrLab with extensive documentation

Disclosure of Interest: None Declared

Low-level mitochondrial heteroplasmy modulates DNA replication, glucose metabolism and lifespan in mice

Hauke Busch[*1], Saleh Ibrahim[1], Misa Hirose[1], Paul Schilf[1], Axel Künstner[1], Anke Fähnrich[1]
[1]Institute of Experimental Dermatology, UNIVERSITY OF LÜBECK, Lübeck, Germany

Secondary topic : Multi-omics

Your abstract : Mutations in mitochondrial DNA (mtDNA) lead to heteroplasmy, i.e., the intracellular coexistence of wild-type and mutant mtDNA strands, which impact a wide spectrum of diseases but also physiological processes, including endurance exercise performance in athletes. However, the phenotypic consequences of limited levels of naturally arising heteroplasmy have not been experimentally studied to date. We hence generated a conplastic mouse strain carrying the mitochondrial genome of an *AKR/J* mouse strain (B6-mtAKR)in a *C57BL/6 J* nuclear genomic background, leading to >20% heteroplasmy in the origin of light-strand DNA replication (OriL). These conplastic mice demonstrate a shorter lifespan as well as dysregulation of multiple metabolic pathways, culminating in impaired glucose metabolism, compared to that of wild-type *C57BL/6 J*mice carrying lower levels of heteroplasmy. Our results indicate that physiologically relevant differences in mtDNA heteroplasmy levels at a single, functionally important site impair the metabolic health and lifespan in mice.

Disclosure of Interest: None Declared

Ribosome-based regulation of cell state transitions

Adrian Lopez Garcia De Lomana[*] [1], Arjun Raman[1], Ulrike Kusebauch[1], Min Pan[1], Serdar Turkarslan[1], Robert Moritz[1], Nitin Baliga[1]
[1]INSTITUTE FOR SYSTEMS BIOLOGY, Seattle, United States

Secondary topic : Quantitative Systems Physiology

Your abstract : The ribosome is a defining structure of all cellular organisms and represents the unique biological process of translation. Although ribosomes are typically represented as molecular assembly lines that constitutively perform coded protein synthesis, translation is a system property that emerges from interactions among diverse types of cellular components, which collectively can control cellular state transitions. The prevailing view that all ribosomes within a cell are structurally identical and functionally equivalent was challenged long ago and is less tenable when examined with modern experimental tools. Here we present a molecular interrogation of *H. salinarum* in total mRNA abundance (RNA-seq), ribosome-associated transcripts (ribosome profiling), and protein abundance (SWATH-MS proteomics) that reveals changes in ribosome composition and regulation across growth phase transition. These data provide evidence that variability in translational systems confers intrinsic regulation of protein synthesis. We found that translational efficiency negatively correlates with absolute transcript abundance, a relationship not apparent for transcript length or half-life. Furthermore, at all levels of expression we consistently observed an increase or decrease in translational efficiency for genes that are transcriptionally upregulated or downregulated, respectively. This observation is in accordance with transcription-translation coupling. Furthermore, systems analysis of environmental and gene regulatory influence networks of *H. salinarum*, *E. coli*, and *S. cerevisiae*, supports a generalized pattern of heterogeneous, environment-specific modularity in translational subsystems across these representative organisms of the three domains of life. We advocate for ribosome-based regulation as a mechanism for steering physiological state transitions and constraining biological evolution.

Disclosure of Interest: None Declared

Atlas of Cancer Signaling Network: a resource of multi-scale biological maps to study disease mechanisms

Luis Cristobal Monraz* [1], Inna Kuperstein[1], Andrei Zinovyev[1], Emmanuel Barillot[1] and Computational Systems Biology of Cancer
[1]Computational Sistems Biology of Cancer, INSTITUT CURIE, Paris, France

Secondary topic : Multi-omics
Your abstract : We present here the second edition of Atlas of Cancer Signaling Network (ACSN2.0, https://acsn.curie.fr). ACSN is a web-based resource of multi-scale biological maps depicting molecular processes in cancer cell and tumor microenvironment. The core of the Atlas is a set of interconnected cancer-related signaling and metabolic network maps. Molecular mechanisms are depicted on the maps at the level of biochemical interactions, forming a large seamless network of above 8000 reactions covering close to 3000 proteins and 800 genes and based on more than 4500 scientific publications. Constructing and updating ACSN involves careful manual curation of molecular biology literature and the participation of experts in the corresponding fields.
The maps of ACSN2.0 are interconnected, the regulatory loops within cancer cell and between cancer cell and tumor microenvironment are systematically depicted. The cross-talk between signaling mechanisms and metabolic processes in the cancer cells is explicitly depicted thanks to new feature of the Atlas: ACSN2.0 is now connected to RECON metabolic network, the largest graphical representation of human metabolism.

The Atlas is a "geographic-like" interactive "world map" of molecular interactions leading the hallmarks of cancer as described by Hanahan and Weinberg. The Atlas is created with the use of systems biology standards and amenable for computational analysis. As of today, ACSN2.0 is composed of 13 comprehensive maps of molecular interactions. There are six maps covering signalling processes involved in cancer cell and four maps describing tumor microenvironment. In addition, there are 3 cell type-specific maps describing signaling within different cells types frequently surrounding and interacting with cancer cells. This feature of ACSN2.0 reflects the complexity of tumor microenvironment.
The resource includes tools for map navigation, visualization and analysis of molecular data in the context of signaling network maps.

Disclosure of Interest: None Declared

Quantitative Systems Physiology - PHYS

Development of an analyzing system of single cell lineage to uncover generation mechanism of the diversity in ATP concentration in Escherichia coli

Masahiro Itabashi[* 1], Takahiro Yamada[1], Akira Funahashi[1], Noriko F. Hiroi[2]
[1]graduate school of science and technology, KEIO UNIVERSITY, Yokohama, [2]Faculty of Pharmaceutical Sciences, Sanyo-onoda City University, Yamaguchi, Japan

Secondary topic : Evolutionary and Ecological Systems Biology

Your abstract : Most of the bacteria maintain the optimal concentration of each essential metabolite in their growth condition.
The difference of those metabolite concentrations causes the phenotypic difference of the bacteria.
These findings imply bacterial populations can acquire the phenotypic diversity dependent on their metabolic condition.
Previous research reported that such phenotypic diversity is observed even within genetically identical bacteria populations.
Moreover, it was also reported that each phenotypically different bacteria shows the different specification of adaptation to the environment.
These facts suggest that phenotypic diversity plays a significant role in cell adaptation to fluctuating environments.
There are generally recognized four hypotheses as the molecular mechanisms to generate such diversity.
To distinguish these mechanisms, we need to observe the behavior of individual cells.
If we can track the phenotype switching during multiple generations of the bacteria at single cell resolution, the specific characteristics originated from the four different mechanisms will appear in the lineage.
However, only a few, specific analyzing systems had been established to track single cell lineage.
Thus, we developed a more generally applicable method for tracking bacteria linage based on the time-series fluorescent images of a popular metabolite, ATP concentration.
We developed the measurement system which enables long-term culture and fluorescence observation by fabricating the microfluidic device.
Also, we cultured a bacteria population under fluorescent microscopy during a long enough term to track at least a few or longer generations.
We got the lineage which includes the information about the change of ATP concentration in E.coli by segmentation and tracking each cell from time-series fluorescent microscopic images for three generations.
We confirmed that a part of bacteria in carbon-starved environment shows high ATP concentrations compared to other cells.
Because ATP is an essential molecule regarding growth, such diversity of ATP concentration may directly contribute to the adaptation strategy of E.coli to the carbon-starved environment.
In future work, we will obtain the lineage of E.coli dependent on ATP concentration in a single cell for longer generations, and analyze the lineage to uncover the molecular mechanism to generate the diversity of ATP concentration, which would connect to the mechanisms of the adaptation mechanisms to fluctuating environment.

Disclosure of Interest: None Declared

Prediction of drug targets through comparison of drug and induced overexpression metabolic profiles

Duncan Holbrook-Smith[*1], Uwe Sauer[1]
[1]Institute of Molecular Systems Biology, ETH Zurich, Zurich, Switzerland

Your abstract :
A crucial step in the development of chemical probes for academic purposes, as well as in drug development, is the initial chemical screen for lead compounds. This process faces the fundamental challenge that there are thousands of potential drug targets, and millions of compounds that could target them. This means that the combinatorial space of drug-target pairings is large enough to preclude exhaustive one-to-one analysis. The ability to make meaningful predictions of drug-target interactions offers to shrink this combinatorial space.

One possibility for the prediction of drug-target interactions leverages the power of high-throughput metabolomics. High-throughput metabolomics allows the generation of detailed phenotypic information regarding the effects of both drug treatments and genetic perturbations on the cell. Both drug treatments and mutations effect their targets by activating or inactivating them, and thus should effect the cellular system in a similar way. In principle, this makes it is possible to predict drug-target interactions based on the similarity of the metabolic profiles of drug and genetic perturbations of the cell.

We compared the metabolic profiles of inducible overexpression strains of receptor-like genes in yeast (*S. cerevisiae*) and those of yeast treated with a library of 1280 compounds. We were able to identify drug treatments that showed metabolic similarity to the genetic perturbations. In addition, the pattern of metabolic similarity between the datasets allowed for the prediction of which drugs may be acting as agonists or antagonists for these target proteins. These results stand as a proof of concept that it is possible to use the comparison of drug and overexpression metabolic profiles to make drug-target predictions.

Disclosure of Interest: None Declared

Universal laws of antimicrobial multi-drug additivity

Dor Russ[* 1], Roy Kishony[1, 2]
[1]Biology, [2]Computer Science, TECHNION - ISRAEL INSTITUTE OF TECHNOLOGY, Haifa, Israel

Your abstract : From natural ecology to clinical therapy, cells are often exposed to mixtures of multiple drugs. Two competing null models are used to predict the combined effect of drugs: response additivity (Bliss) and dosage additivity (Loewe). Here, noting that these models diverge with increased number of drugs, we contrast their predictions with growth measurements of four phylogenetically distant microbes including *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis and Saccharomyces cerevisiae*, under combinations of up to 10 different drugs. In all species, as the number of drugs increases, Bliss maintains accuracy while Loewe systematically loses its predictive power. The total dosage required for growth inhibition, which Loewe predicts should be fixed, steadily increases with the number of drugs, following a square root scaling. This scaling is explained by an approximation to Bliss where, inspired by RA Fisher's classical geometric model, dosages of independent drugs adds up as orthogonal vectors rather than linearly. This dose-orthogonality approximation provides results similar to Bliss, yet uses the dosage language as Loewe and is hence easier to implement and intuit. The rejection of dosage additivity in favor of effect additivity and dosage orthogonality provides a framework for understanding how multiple drugs and stressors add up in nature and the clinic.

Disclosure of Interest: None Declared

Application of mass spectrometry based metabolomics and fluxomics for biotechnological strain improvement

Dieter Weber[* 1], Ulf Liebal[1], Birgitta Elisabeth Ebert[1], Jörg Mampel[2], Lars Mathias Blank[1]
[1]RWTH AACHEN UNIVERSITY, Aachen, [2]BRAIN AG , Zwingenberg, Germany

Your abstract :
Application of mass spectrometry (MS), a highly sensitive high-throughput analytical technique for the purpose of metabolic engineering of organisms may not seem obvious in the first instance. Biotechnology approaches are typically associated with terms like biochemistry, gene technology, molecular biology, process engineering, up- and downstream processing, whereas the analytical part is usually quite limited and often focuses on product(s) of interest just to determine the titer, yield and productivity of the system. However, advances in the omics fields show growing influence on biotechnology and systems engineering. Especially the availability of gene and genome sequences as well as access to modern sequencing techniques have proven to be extremely valuable. Yet, it took about three decades of genomics research to develop techniques and services currently used in laboratories on a daily basis.

MS has proven itself as the method of choice in many other, later emerged omics branches (proteomics, glycomics, metabolomics, lipidomics, fluxomics) since it allows, especially in hyphenation with chromatography, the identification/quantification of many different analytes. However, already due to the higher complexity of other than nucleic acid biomolecules (number of distinct building blocks and combinations) it is to anticipate from the analysis technique to be more sophisticated, data interpretation more challenging. Definitely MS is more complex and requires skilled personal capable to adjust the method depending on target compounds and sample origin. This might be the reason why, although practiced for decades, MS still is less routine. Yet, MS can provide much deeper insights into cellular processes and help to understand biological systems or resolve why a genetic modification does not lead to the intended effect. Especially for the latter, estimation of metabolic pool sizes (quantitative metabolomics) or flux rates within the cells (^{13}C metabolic flux analysis) are very helpful.

We apply GC-MS and MS/MS to study metabolite compositions and metabolic fluxes in yeast and bacteria to identify possible bottlenecks and targets for future strain improvements in collaboration with industry partners. Our work include definitions of stoichiometric metabolic models, cultivation of microorganism, developing of sample preparation techniques (e.g. different combination of quenching and metabolite extraction, derivatization) and GC-MS methods (fullMS, SIM, MRM).

Disclosure of Interest: None Declared

Analyzing the potential productivity of CAM photosynthesis using mathematical modeling

Antonio Rigueiro Mesejo[* 1], David Heckmann[2], Martin Lercher[1]
[1]Institute for Computer Science and Department of Biology, University Heinrich Heine Dusseldorf, Dusseldorf, Germany, [2]Department of Bioengineering, University of California at San Diego, San Diego, United States

Secondary topic : Quantitative Systems Physiology

Your abstract : CAM (Crassulacean Acid Metabolism) is one of the three major photosynthetic pathways. It evolved independently from C_3 many times and accounts for 7% of currently known plant species. CAM plants absorb CO_2 during the night, which is stored in the plant cell vacuoles as malate; CO_2 is released into the cytosol during the day, when it is fixed by the enzyme Rubisco. CAM evolves in niches where water is scarce and is usually associated with low growth rates. However, well-watered CAM plants have been reported to have productivities similar or even surpassing C_3 plants, awakening interest into engineering the pathway into drought-resistant crops able to exploit marginal lands.

To predict plant productivity in the C_3-CAM continuum, we developed a general *in silico* model that incorporates the biochemical pathways of C_3 and CAM photosynthesis, leaf gas transfer, thermal balance, and water flow from the soil through the plant. Depending on the biochemical and physiological parameterization, the model describes the physiology of C_3, CAM, or intermediate photosynthesis. The productivity of a particular variety is approximated by the total amount of photosynthesized sugars. The predictions are validated using gas exchange data for C_3 and CAM plants.

The model allows us to compare the photosynthetic productivity of different configurations in the C_3-CAM continuum under diverse conditions of rainfall, solar irradiation, and nitrogen availability. Our simulations show that CAM photosynthesis presents reduced photorespiration, an unavoidable side reaction of Rubisco, where oxygen is used instead of carbon dioxide, leading to a net loss of energy and carbon. Plants combining CAM and partial C_3 stomatal opening can achieve productivity values even higher than C_3 plants. Furthermore, we find that CAM plants are more efficient than C_3 plants at concentrations of atmospheric CO_2 lower than the current ones. Finally, the model results indicate that the maximum productivity of CAM plants requires some degree of leaf succulence to allow enough volume for the accumulation of malate; our results provide the first quantitative explanation for the observed co-evolution of succulence and CAM.

Disclosure of Interest: None Declared

Cellular resource allocation and metabolic trade-offs during diurnal phototrophic growth

Ralf Steuer* [1]
[1]Institute for Theoretical Biology, Humboldt-University of Berlin, Berlin , Germany

Secondary topic : Modelling Networks and Circuits

Your abstract : Cyanobacteria are phototrophic microorganisms of global importance. As evolutionary inventors of oxygenic photosynthesis and as precursors of modern chloroplasts, cyanobacteria have influenced the Earth's biochemistry like no other organism. In addition to their glorious past, cyanobacteria also hold great promise for the future: the potential offered by cyanobacteria will undoubtedly play a major role in mastering the challenges of the 21st century – from securing global food supply to the synthesis of renewable raw materials. As yet, however, fundamental questions regarding the metabolic principles of cyanobacterial phototrophic growth are not resolved: How are metabolic, photosynthetic, and ribosomal proteins optimally partitioned during phototrophic growth? What is the highest growth rate a cyanobacterium can attain?

To answer these fundamental questions of cyanobacterial growth physiology requires a combination of computational modelling and wet-lab experiments. The contribution will present our recent efforts to describe cyanobacterial phototrophic growth as a cellular resource allocation problem and estimate the costs and benefits of all metabolic constituents of a cyanobacterial cell. Of particular interest are the cellular organization that enables fast phototrophic growth and the corresponding intracellular limits on phototrophic growth rates. The model-derived optimal metabolite partitioning during diurnal growth is in good agreement with experimental findings and provides insight into optimal metabolic allocation during diurnal growth – with implications for ecology, CO2 sequestration and applications in green biotechnology.

References:

1. Reimers AM, Knoop H, Bockmayr A, Steuer R (2017) Cellular trade-offs and optimal resource allocation during cyanobacterial diurnal growth. Proc Natl Acad Sci U S A. Pii: 201617508. doi: 10.1073/pnas.1617508114.

2. Westermark S and Steuer R (2016) Toward multiscale models of cyanobacterial growth: a modular approach. Front. Bioeng. Biotechnol. 4:95. doi: 10.3389/fbioe.2016.00095

3. Knoop H, Gruendel M, Zilliges Y, Lehmann R, Hoffmann S, Lockau W, Steuer R (2013) Flux balance analysis of cyanobacterial metabolism: The metabolic network of Synechocystis sp. PCC 6803. PLoS Comput Biol 9(6): e1003081. doi:10.1371/journal.pcbi.1003081

Disclosure of Interest: None Declared

Global gene-expression regulation as a response to nitrogen limitation in fission yeast

Istvan T. Kleijn[* 1, 2, 3], Amalia Martínez Segura[1, 3], Miles Priestman[1, 2, 3], François Bertaux[1, 2, 3], Vahid Shahrezaei[2], Samuel Marguerat[1, 3]
[1]MRC London Institute of Medical Sciences, [2]Department of Mathematics, [3]Institute of Clinical Sciences, Imperial College London, London, United Kingdom

Secondary topic : Multi-omics

Your abstract : Unicellular organisms use nutrients from their environment as energy sources. Variations in the quantity and quality of these nutrients have a profound impact on the cell physiology that translate into changes in metabolism, growth and gene expression. To understand this intricate process, we have analysed the translational and transcriptional resource allocation of the fission yeast *Schizosaccharomyces pombe* in different growth environments.

We have cultured cells at steady-state in turbidostats in a series of growth media using different single amino-acids as nitrogen sources. This setting supported division rates ranging from 0.05 to 0.28h^{-1}. From these cultures we have generated label-free proteomics and RNA-seq datasets, leading to accurate quantification of ~1500 proteins and ~5000 transcripts across all conditions.

We have used this combined dataset to monitor proteome and transcriptome allocation as a function of division rate, and to define nitrogen-source specific gene expression programmes. We have found that the linear correlations between the division rate and the ribosomal protein fraction, observed in prokaryotes and budding yeast, is also present in fission yeast at both the protein and mRNA levels. However, the total proteome fraction of *S. pombe* proteins involved in cytoplasmic translation ranged between 6-12% only, which is lower than reported for other organisms. Interestingly, transcript abundance of subunits of the RNA polymerases (RNAP) I and III increased linearly with the division rate, while transcripts specific to polymerase II remained constant. This suggests that the mechanisms coordinating ribosomal RNA (RNAPI) and protein (RNAPII) production with division rate differ. Furthermore, around half of the fission yeast proteome (by mass) did not respond to the division rate; instead, many genes were overexpressed in few growth conditions. The total proteome mass fraction of these medium-specific proteins decreased linearly with increasing growth rate under nitrogen limitation, pointing towards the existence of condition-dependent allocation strategies.

These results will inform the interpretation of proteome allocation growth laws and help the comparison of allocation strategies across the tree of life. Furthermore, they will allow the development of coarse-grained models of cell physiology that will provide a framework in which detailed models of cellular subsystems, such as the cell cycle, can be embedded.

Disclosure of Interest: None Declared

Comprehensive mapping of the protein-metabolite interactome of E. coli central carbon metabolism

Maren Diether[*1], Yaroslav Nikolaev[1], Frederic Allain[1], Uwe Sauer[1]
[1]ETH ZURICH, Zürich, Switzerland

Secondary topic : Multi-omics

Your abstract :

Protein-metabolite interactions play an important role in the regulation of many cellular processes. In particular, metabolic enzymes are subject to extensive regulation by metabolites, ensuring that molecular building blocks and energy equivalents are produced in any given environment. While enzyme regulation by metabolites has been investigated for decades, we have a fragmented picture at best, and a systematic and consistent method to probe them is lacking.

Here, we present the first systematic application of a recently described ligand-detected nuclear magnetic resonance (NMR) method to comprehensively map protein-metabolite interactions in *E. coli* central metabolism. Specifically, we assayed 29 enzymes towards their ability to bind 55 intracellular metabolites. In total, we detected 95 interactions including 22 previously known catalytic/regulatory interactions at a false discovery rate of 0.05. By investigating the chemical similarity between substrates/products of the enzymes and interacting metabolites, we predict that about half of the newly detected interactions are allosteric (i.e. binding of a regulatory metabolite to a site other than the active site), indicating that the total number of allosteric interactions in the tested set is at least twice as high as previously anticipated. Out of all tested metabolites, purine nucleotides (GTP, AMP and ATP) exhibited most interactions, while 50 % of all metabolites did not interact with any enzyme. In contrast, enzymes interacted with up to 11 metabolites, and only five proteins did not exhibit any metabolite binding. The regulatory function of several newly discovered interactions was confirmed by enzyme assays. In combination with other data sets, we thus present the so far most comprehensive protein-metabolite interactome of any biological subnetwork.

Disclosure of Interest: None Declared

Long-term non-genetic adaptation of antibiotic-stressed Escherichia coli

Miki Umetani[*1,2], Miho Fujisawa[1], Chikara Furusawa[2,3], Yuichi Wakamoto[1,3,4]
[1]Department of Basic Science, Graduate School of Arts and Sciences, The University of Tokyo, Tokyo, [2]Center for Biosystems Dynamics Research, RIKEN, Osaka, [3]Universal Biology Institute, [4]Research Center for Complex System Biology, The University of Tokyo, Tokyo, Japan

Secondary topic : Single-cell Systems Biology

Your abstract : Antibiotic-resistant bacteria could sometimes emerge purely phenotypically without genetic mutations. However, the detailed histories of single cells that gain resistant phenotypes and the inheritance stability of acquired phenotypes remain uncertain. Here, we examined the single-cell dynamics of antibiotic-resistant bacteria that emerged in a clonal population. We observed behaviors of individual cells in a clonal population exposed to an antibiotic using a custom microfluidics device. Isogenic cells of *E. coli* harboring a chloramphenicol resistance gene (*cat*) were exposed to the minimum inhibitory concentration (MIC, 30 μg/ml) of chloramphenicol (Cm) in the microfluidic device. We found that the drug exposure significantly suppressed the growth of all the cells in the population, but a fraction of the cells in the population gradually recovered stable growth within three days of continuous exposure, continued dividing, and stably inherited the resistance to the descendants for over 100 generations. We removed the drug once and exposed the descendants of the survived cells to 30 μg/ml Cm again after incubating the cells under drug-free conditions for about 8 h, finding that all of them were killed. This result suggests that the enhanced resistance is lost once the drug is removed from the environment, and that the observed adaptation is achieved non-genetically without resistant mutations. Additionally, we found that cells growing stably at 30 μg/ml Cm were resistant even to the Cm concentration higher than MIC. The result suggests that antibiotic resistance levels can be modulated and inherited epigenetically.

Disclosure of Interest: None Declared

Single-cell Systems Biology - CEL

Computational screening of signature genes for rare cell population involved during neurogenesis

Mohit Navandar[*1], Constance Vennin[2], Susanne Gerber[1]
[1]Faculty of Biology, Institute for Developmental Biology and Neurobiology AND Center for Computational Sciences in Mainz,, Johannes Gutenberg-University, Staudinger Weg 9, 55128, Mainz, [2]Institute of Physiological Chemistry,, University Medical Center of the Johannes Gutenberg University, Duesbergweg 6, 55128,Mainz, Germany

Secondary topic : Developmental Systems Biology

Your abstract : Neuronal development involves symmetric and asymmetric division of neuroepithelial cells, which results in different cell population. Despite our understanding of the different cell types and its signature genes involved in the neuronal development, we still lack understanding of certain rare populations and its signature genes. Fortunately, single cell genomics provides an opportunity to identifying and deciphering the function of such rare populations. Hence, it is essential to undertake research for characterizing confident signature gene(s) for rare cell populations.

Towards this, we used currently available single cell RNA-sequencing (scRNA-seq) datasets for hippocampus area of mouse adult and embryonic stages from public domains. After processing these datasets, we could identify expression pattern characteristic for particular cell population. We further applied statistics and mathematical approaches to screen the potential signature genes. To gain confidence on the predicted signature genes, we further implemented machine learning methods such as support vector machine and neuronal networks. Using these approaches, we could predict the specific signature gene(s) for particular cell populations.

We will present these results as well as validation approaches. Validation approaches like fluorescence activated cell sorting (FACS) based on the predicted signatures followed by scRNA-seq will be implemented. Predictions gained from analyzing publicly available scRNA-seq datasets will be discussed as along with results from in-house experiments studying the fate of these cells during mouse brain development. Overall, we believe that our study substantially enlightens the understanding of molecular signature for rare cell population involved in neurogenesis.

Keywords: neurogenesis, single cell RNA sequencing, machine learning, FACS, signature genes

Disclosure of Interest: None Declared

Monitoring of flagellar motility using microfluidic technology

Merve Yuce[*1], Elif Ozkirimli Olmez[1], Berna Sariyar Akbulut[2], Kutlu Ulgen[1] and Ulgen Research Group

[1]Chemical Engineering, Bogazici University, [2]Bioengineering, Marmara University, Istanbul, Turkey

Secondary topic : Quantitative Systems Physiology

Your abstract : Flagella have been regarded as important virulence factors since they contribute to motility by allowing bacteria to move towards favorable environments such as new hosts, habitats or niches [1]. Microfluidic technology is used to reduce sample consumption, shorten heat and mass transfer times and also provide a controlled environment to analyze individual cells [2]. This system provides the monitoring of dynamics at a single cell level and is shown to be a highly simple and reliable alternative to plate based motility assays that are sensitive to solid phase composition, as well as traditional microscopic techniques that use bacterial samples trapped between microscope slides. Microfluidic chips enable us to observe cells continuously and to study the effects of drugs on living cells. In the current study, we used 10 µL chips made of thermoplastic material and monitored the motility of the gram negative *E. coli* K12 compared to non-motile *E. coli* K12 HCB137 cells (Δflagella) strain in zeonor reaction chamber under an inverted microscope. It was also possible to follow the growth and division of the non-motile *E. coli* K12 HCB137 cells. Time-lapse images of *E. coli* K12 cells were captured and processed to calculate swimming speeds. Thereafter, gram positive bacteria, *B. marmarensis* cells, which have Na^+ dependent flagellar rotor were treated with amiloride that inhibits sodium channel, resulting in non-motile cells as expected. *B. subtilis* 168 has both Na^+ dependent and H^+ dependent flagellar rotors but H^+ dependent rotor is dominant. When we treated these cells with amiloride, the motility is inhibited on the contrary of our expectations. Therefore, quantitative real-time PCR analysis will be performed in order to understand which genes associated with motility were upregulated or downregulated after amiloride treatment. Our findings demonstrate that this lab-on-a-chip device that uses microfluidic technology is a simple, accurate, and quick alternative to classical plating to investigate the integrity of flagellar motility and inhibition of motility via drugs.

Keywords : Flagellar motility, microfluidic technology, live-cell imaging

References

[1] Q. Duan, M. Zhou, L. Zhu, and G. Zhu, “Flagella and bacterial pathogenicity,” *J. Basic Microbiol.*, vol. 53, no. 1, pp. 1–8, 2013.

[2] C. Yi, C. Li, S. Ji, and M. Yang, “Microfluidics technology for manipulation and analysis of biological cells,” *Anal. Chim. Acta*, vol. 560, pp. 1–23, 2006.

Disclosure of Interest: None Declared

Sigma factor mediated memory

Christian Schwall[* 1], Torkel Loman[1], Bruno Martins[1], Toby Livesey[1], Cassandra Villava[1], Ting Wang[1], Vassili Kusmartsev[1], James Locke[1]
[1]The Sainsbury Laboratory, University of Cambridge, Cambridge, United Kingdom

Secondary topic : Single-cell Systems Biology

Your abstract : Bacteria can quickly adapt to changing environmental conditions with the help of alternative sigma factors. It remains unclear how these alternative sigma factors respond to their specific stresses and how their response dynamics arise from the underlying genetic network. Here, we investigated the single cell response dynamics of the *B. subtilis* extracytoplasmic function sigma factor σ^V in response to lysozyme stress. To do this we used a combination of single cell time-lapse microscopy, microfluidics, and mathematical modelling. We observed that in response to lysozyme stress *B. subtilis* heterogeneously activated σ^V, with some cells not turning on the pathway until hours after the stress application. However, after a stress holiday of several generations the σ^V activation was synchronized in response to lysozyme. Thus, the σ^V circuit can act as a simple form of memory. By perturbing and mathematically modelling the circuit we found that this behaviour results from σ^V's positive auto – regulation of its own operon and the proteolytic destruction of σ^V's anti-sigma factor.

Disclosure of Interest: None Declared

Expression variability of B-cell surface proteins displays genetic variation among humans

Gérard Triqueneaux[1], Claire Burny[1], Orsolya Symmons[1], Stéphane Janczarski[1], Henri Gruffat[2], Gael Yvert[* 1]

[1]Laboratory of Biology and Modeling of the Cell, CNRS, ECOLE NORMALE SUPERIEURE DE LYON, [2]Centre International de Recherche en Infectiologie, INSERM, CNRS, ECOLE NORMALE SUPERIEURE DE LYON, Lyon, France

Secondary topic : Systems Medicine

Your abstract : Cell-to-cell gene expression variability - also called 'noise in gene expression' - has been associated to several important biological processes, including differentiation or persistence to drug treatments. We previously showed that, in yeast, the extent of expression variability depends on the genotype: some DNA variants, when present in all cells, can increase variability in the population of cells. Here we describe cell-to-cell expression variability of four cell-surface proteins in human lymphoblastoid cell lines from unrelated healthy individuals. Using immunofluorescent flow-cytometry, we quantified expression levels in single-cells from these lines. We observe substantial variation of the degree of cell-cell variability, with cases of bimodal expression that radically differs between the lines. Using subcloning and clonality genotyping, we show that variability can be observed in the context of monoclonal cell lines. By generating multiple lines from two donors, we find that variability differs more between- than within-individuals. Genetic mapping reveals *cis*-acting SNPs marginally associated with the extent of expression variability. Our results show that the statistical properties of human gene expression are finely tuned by standing genetic variation.

Disclosure of Interest: None Declared

Predicting the future direction of cell movement with convolutional neural networks

Shori Nishimoto[*1], Yuta Tokuoka[1], Noriko Hiroi[2], Akira Funahashi[3]
[1]Graduate School of Science and Technology, Keio University, Yokohama, [2]Faculty of Pharmaceutical Sciences, Sanyo-onoda City University, Yamaguchi, [3]Department of Biosciences and Informatics, Keio University, Yokohama, Japan

Your abstract : Image-based deep learning, such as Convolutional neural networks (CNNs), has recently been applied to the bioimage analysis, producing impressive results, especially in the cell classification. These application cases of CNNs remain at the classification of current cell state from the image. However, recent studies demonstrate that current and/or past cell shape, which dynamically changes, influences the future cell fate. An interesting question is whether CNNs could predict the future cell fate based on current and/or past cell shape.
Here, we focused on dynamic cell movement where current and/or past cell shape can influence the future cell fate. Our hypothesis was that CNNs could learn such cell shape and predict the future direction of cell movement from a single image patch of a cell at a certain time.
We prepared image datasets from time-lapse phase-contrast microscopic images of cell movement of NIH/3T3 cells and U373 cells, respectively. Using these datasets, we trained and validated CNN models to predict the future direction of cell movement from a single image patch of a cell at a certain time. CNN models achieved Mean Classification Accuracy (MCA) of 85.8% for NIH/3T3 cells, 85.4% for U373 cells.
Furthermore, to reveal how and why CNN models could predict the future direction, we visualized the features on the cell images that were learned by CNN models and contributed to their prediction. As a result, we identified the morphological features, such as the protrusions, the trailing edge, and the polarity of cell shape, which are reported to determine the direction of cell movement.

Our results indicated that CNNs have the potential to predict the future cell fate from current and/or past cell shape. Results of visualization also indicated that the morphological features influential in the future cell fate could be identified in a top-down manner with CNNs.

Disclosure of Interest: None Declared

Benchmarking of unsupervised cytometry data analysis methods for the comparison of population

Nicolas Sapay[*1], Benoît Beitz[2], Benoit Courbon[1], Ana Delgado[1]
[1]BIOASTER, Lyon, [2]BIOASTER, Paris, France

Your abstract : Cytometers allow high dimensional quantitative measurement of single cells characteristic. At the beginning, the cell analysers were limited to five parameters. Recent progress in flow and mass cytometry now permits the analysis of a larger panel of parameters, from ten to more than forty. Traditionally, analysis of cytometry data is performed manually, plotting cells in one or two dimensional plots on specific markers. This method is time consuming, subjective and hard to reproduce. Consequently, new data analysis methods were rapidly developed. Their objective was to handle the higher dimensionality of the data and to improve the reproducibility of the results. Now, several methods are available. However, the lack of standard data sets have limited their systematic benchmarking.
In our institute, we face more and more studies where we tried to identify cells subsets in sample or to monitor immune response on different groups of samples. The objective is to establish the variation in cell composition, i.e. a comprehensive immunophenotyping of the white blood cells of each group. We choose to handle this question by an unsupervised approach, where the cells of a sample are first clustered as a function of the markers expressed on their surface, and then the features of each cluster are extracted to assess the cell type.
After a thorough review of the literature, we have selected three methods belonging to three methodological fields: a graph based method, a density based method and a hierarchical clustering method. Two of them were initially developed to treat flow cytometry data in a low-dimensional space, i.e. with few markers. The three methods were evaluated on two manually annotated data sets: a homogeneous mouse data sets including 10 individuals and a human data set of 3 individuals tested in 2 conditions. The clustering results where compared to those manual annotations using the F-measure, the normalized mutual information and the adjusted rand index. The benchmark produces different results for each data set at the sample scale. At the population scale, the graph base approach allows the comparison of several groups of samples, when chained to a simple hierarchical clustering method.
These results allow us to develop a first automated pipeline to analyze the cytometry data at the scale of a whole study.

Disclosure of Interest: None Declared

An integrated platform for dynamic microfluidics based single-cell experimentation

Christian C. Sachs[1], Dietrich Kohlheyer[1], Wolfgang Wiechert[1], Katharina Nöh[* 1]
[1]IBG-1: Biotechnology, Forschungszentrum Jülich GmbH, Jülich, Germany

Secondary topic : Methodological developments for Systems Biology

Your abstract : Phenotypic heterogeneity, the "non-genetic" variation that is observed between cells in isogenic populations in response to changes of their environment, is an intriguing phenomenon that affects the cells' fitness and the survival of a population as a whole. In this context, microfluidic lab-on-chip experimentation combined with time-lapse imaging provides the unique ability to follow the fate of single cells over time frames of hours to weeks. Together with the precise control of the environmental parameters in terms of, for instance, nutrient availability or temperature, a superior information quality is attained. Connecting live-image analysis to control the microfluidic settings unlocks flexible programmable experimentation.

Here we present an automated platform for dynamic microfluidics based microbial single-cell experimentation. The platform integrates a high-level programmable control of the microscope with peripherals like syringe pumps and valves. The control unit of the platform is connected with a deep learning based image analysis module, which is capable of live evaluating the accruing image stacks. User interaction takes place remotely via a web interface. Moreover, a lightweight scripting interface facilitates a convenient conceptualization of feed-back experiments. We demonstrate the functionality of the platform with the biotechnological platform host *C. glutamicum,* whose growth rate is feedback-controlled by shifts in nutrient availability. Joining these data with quantitative models could improve our understanding of the mechanisms underlying phenotypic heterogeneity and how these might be used to improve biotechnological processes.

Disclosure of Interest: None Declared

Spatial unification of coupling interactions between EGFR and PTPs establishes a growth factor sensing network

Angel Stanoev[*1], Amit Mhamane[1], Wayne Stallaert[1], Rabea Stockert[1], Yannick Brüggemann[1], Philippe Bastiaens[1], Aneta Koseska[1]
[1]Systemic Cell Biology, MAX PLANCK INSTITUTE OF MOLECULAR PHYSIOLOGY, Dortmund, Germany

Secondary topic : Modelling Networks and Circuits

Your abstract : The epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase whose response to growth factor stimulation leads to diverse cellular behaviors. The phosphorylation dynamics of EGFR is regulated by an intricate balance between its autocatalytic activation and the counteracting dephosphorylation of protein tyrosine phosphatases (PTPs), which are distributed in diverse cellular locations. By combining single-cell imaging and dynamical systems approaches we identify how specific EGFR activity modes emerge from the distinct, spatially regulated interaction motifs with PTPs. The EGFR-PTPRG interactions at the plasma membrane, shaped into a double-negative feedback motif, provide the means for robust switch-like EGFR activation. Vesicular EGFR dynamics, on the other hand, gives rise to the EGFR-PTPN2 negative feedback that suppresses phosphorylation of the recycling receptors in the perinuclear area as they travel to the plasma membrane, thereby resetting the system. The spatial unification of these diverse coupling interactions with the PTPs through the vesicular trafficking thus forms a distinct EGFR-PTP system that coordinates the sensing and phosphorylation response of EGFR to time-varying growth factor signals.

Disclosure of Interest: None Declared

Single cell data generation for the calibration and development of a multiscale model of effector and memory CD8 T cell differentiation

Shaoying Wang[*1,2], Daphne Laubreton[1], Simon Girel[3,4], Fabien Crauste[5], Olivier Gandrillon[3,6], Christophe Arpin[1], Jacqueline Marvel[1]

[1]Centre International de Recherche en Infectiologie, INSERM, U1111, Universite´ Claude Bernard Lyon 1, CNRS, UMR5308, E´cole Normale Supe´rieure de Lyon, Universite´ de Lyon, lyon, France, [2]Shanghai Key Laboratory of Regulatory Biology, Institute of Biomedical Sciences and School of Life Sciences, East China Normal University, shanghai, China, [3]Inria team Dracula, Inria, 56 Boulevard Niels Bohr, Villeurbanne, [4]Université Claude Bernard Lyon 1, CNRS UMR 5208, Institut Camille Jordan, 43 blvd. du 11 novembre 1918, F-6962 Villeurbanne Cedex, lyon, [5]Department of Mathematics,CNRS UMR 5251,University of Bordeaux, Talence, [6]Laboratory of Biology and Modelling of the Cell, École Normale Supérieure de Lyon, 46 allée d'Italie, lyon, France

Secondary topic : Multiscale Systems Biology

Your abstract : Following acute infection, the activation of naive CD8 T-cells by antigen presenting cells triggers their proliferation and differentiation up to the memory state. We are aiming at building a multiscale dynamical model of this response.

We recently described a refined version of such a model where cells are described as agents evolving and interacting in a 2D environment, and a set of differential equations, embedded in each cell, models the regulation of intra and extracellular proteins involved in cell differentiation ([1]).

The internal molecular network is driven by T-bet and eomesodermin (EOMES), two T-box transcription factors that have crucial roles in the formation and function of effector and memory CD8+ T cells. Furthermore, an IL-2 autocrine loop was shown to be a main driver of the model response ([2]).

In order to better understand and parametrize our *in silico* model, we decided to acquire expression data at the relevant single-cell scale, for three major actors of the response that are T-bet, EOMES and CD25 (the α-chain of the Il-2 receptor).

We studied the impact of various in vitro activation conditions on the expression levels of those proteins by activated CD8 T cells. The generation of different effector and memory subsets in these different conditions will also be monitored. Our preliminary results indicate that antigen and IL-2 concentration can drive the generation of different qualities of effector cells that we are currently characterizing.

We will then use the quantitative data generated at the single cell level to improve the parametrization and the predictive ability of our multiscale model.

1. Girel, S., et al. BioRxiv, 2018. **doi: https://doi.org/10.1101/345165**.
2. Gao, X., et al. BMC Syst Biol, 2016. **10**(1): p. 77.

Disclosure of Interest: None Declared

Systems Medicine – MED

CausalR: extracting mechanistic sense from genome scale data

Glyn Bradley[*1]
[1]Computational Biology and Statistics, GSK, Stevenage, United Kingdom

Secondary topic : Methodological developments for Systems Biology

Your abstract : With the continuing increase in the generation of genome-wide expression datasets, the limitations of commonly used interpretation methods, such as Gene Ontology classification, Gene Set Enrichment Analysis and pathway mapping, have become increasingly apparent. They are useful for classifying endpoints extracted from a new experiment but are of limited use at uncovering the mechanisms that led to the observed changes.
Causal reasoning (causal network analysis) can be used to predict the root cause of observed effects. It requires a causal graph, in the form of a signed, directed interaction network, describing the system under study. Observed endpoints serve as a starting point for the analysis. A reasoning algorithm is then used to track back through the causal graph to find points of convergence that maximally and accurately explain the differential regulatory pattern seen across the endpoints. In a biological analysis these points are likely to be key upstream regulators of the observed endpoints, and so for example in a drug discovery environment may represent the best targets for reversing the observed endpoints.
Here we present CausalR, a biologically focused causal reasoning implementation coded in the popular statistical language R, and made available from the Bioconductor project CausalR builds upon existing methodology and provides an enhanced, open source alternative to commercial software.
We show application to epithelial focused COPD target discovery, demonstrating the ability of CausalR to extract enhanced insights from public datasets.

Reference
CausalR: extracting mechanistic sense from genome scale data.
Glyn Bradley; Steven Barrett
Bioinformatics 2017, Volume 33, Issue 22, 15 November Pages 3670–3672,

Disclosure of Interest: G. Bradley Conflict with: Employee of GSK

Quantitative modelling of the NF-κB system as a basis for the analysis of pathway mutations

Jana Wolf[*] [1] and Mathematical Modelling of Cellular Processes
[1]MAX-DELBRUECK-CENTER FOR MOLECULAR MEDICINE, Berlin, Germany

Secondary topic : Modelling Networks and Circuits

Your abstract : The NF-κB pathway regulates fundamental cellular processes such as cell differentiation, proliferation and survival. Aberrant activation of the pathway, e.g. by mutations, can lead to various types of cancer and inflammatory diseases. The signaling system has a complex structure and consists of a canonical and a non-canonical branch. These can be activated by a range of stimuli and lead to the activation of different members of the NF-κB transcription factor family. Interestingly, both signaling branches act on different time scales but are linked via shared pathway components and target gene expression. In the past, we employed a combination of quantitative, time-resolved mass-spectrometry approach and computational modelling to elucidate the mechanisms of the NF-κB precursor processing. This revealed hitherto unknown interdependencies of the canonical and non-canonical signaling branches on the precursor level. We now developed a first dynamical model for the non-canonical NF-κB pathway and used it for an analysis of signaling characteristics and mutation effects.

Disclosure of Interest: None Declared

Differential co-expression network analysis presents the molecular signatures of invasiveness in non-functional human pituitary adenoma

Busra Aydin[*1], Kazim Yalcin ARGA[1]
[1]BIOENGINEERING, MARMARA UNIVERSITY, ISTANBUL, Turkey

Secondary topic : Multi-omics

Your abstract : Non-functional pituitary adenomas (NFPAs) are tumors with clinically challenging features since they have sneaky progression and influenced by a complex network of gene interactions. Therefore, revealing the relationships between genes and NFPA is essential to contribute further knowledge on tumor biology. Gene co-expression network analysis is an outstanding approach for elucidation of co-expressed groups of genes from large and complex mRNA expression datasets. In this study, we carried out differential co-expression network analyses of genes to identify potential systems biomarkers for NFPA prognosis and sub-typing. As a result, we identified a module of 13 genes to categorize the patients into two groups as invasive and non-invasive NFPA with high specificity and sensitivity. In addition, prognostic core module genes were investigated to be associated with progression and prognosis of pituitary adenoma related cancers, as well. *In silico* validation of core module across other associated cancers (i.e., brain tumors and glandular based cancers) are also performed. Our results provide the evidence on featured gene module which may play a prominent role in NFPA prognosis and sub-typing as effective biomarkers and therapeutic targets in the future.

Disclosure of Interest: None Declared

Systems biology of herbal medicine: elucidating the transcriptome and metabolome signature of the complex effect of traditional Japanese medicine

Akinori Nishi[*] [1], Katsuya Ohbuchi[1], Hirotaka Kushida[1], Chika Shimobori[1], Noriko Kaifuchi[1], Takashi Matsumoto[1], Hitomi Kanno[1], Makoto Zushi[1], Masahiro Yamamoto[1], Haruo Kuroki[2], Shigeki Nabeshima[3], Ayako Yachie[4], Yukiko Matsuoka[4], Hiroaki Kitano[4]
[1]TSUMURA Kampo Research Laboratories, TSUMURA&CO., Ibaraki, [2]Sotobo Children's Clinic, Medical Corporation Shigyo-no-kai, Chiba, [3]General Medicine, Fukuoka University Hospital, Fukuoka, [4]The Systems Biology Institute, Tokyo, Japan

Secondary topic : Multi-omics

Your abstract : Traditional herbal medicine comprises multiple herbal ingredients, the combination of which is regarded as key to their pharmacological efficacy. For example, maoto, a traditional Japanese medicine (*Kampo*) that is prescribed for influenza-like symptoms, contains four different herbs: Armeniacae Semen, Glycyrrhizae Radix, Cinnamomi Cortex, and Ephedrae Herba. In a previous study, we showed that maoto ameliorated both the surge in proinflammatory cytokines and symptoms of disease in a rat model of acute inflammation. Maoto broadly affected lipid mediator responses and modulated the balance of proinflammatory and anti-inflammatory lipid mediators in the plasma metabolome. However, the pharmacological action of maoto as a whole remedy remains unknown, although the effect of the primary active ingredient "ephedrine" (from Ephedrae Herba) and several major ingredients in each herb have been evaluated. In this study, we have further examined the combinatorial effect of maoto by comparing metabolomic and transcriptomic properties among ephedrine, a mixture of major ingredients ("toy-maoto"), and maoto in a rat model of polyI:C-induced inflammation. By analyzing the data using gene set enrichment analysis (GSEA), weighted gene co-expression network analysis (WGCNA), and lipid mediator centric metabolomics pathway enrichment, we found that the single ingredient ephedrine, the mixture of ingredients, and the original maoto showed varied efficacy in ameliorating the polyI:C-induced inflammatory responses. Whereas ephedrine contributed mainly to inhibiting major proinflammatory factors in the early phase of the inflammatory response, toy-maoto and maoto affected broader pathways such as the immune response and cell cycle for an extended period. These results suggest that several ingredients of maoto contribute to the complex process of resolving inflammatory responses. In summary, we have demonstrated that the specific pharmacological properties of a traditional Japanese medicine are exerted by a mixture of herbs and not by a single ingredient.

Disclosure of Interest: A. Nishi Conflict with: Employed by Tsumura & CO., K. Ohbuchi Conflict with: Employed by Tsumura & CO., H. Kushida Conflict with: Employed by Tsumura & CO., C. Shimobori Conflict with: Employed by Tsumura & CO., N. Kaifuchi Conflict with: Employed by Tsumura & CO., T. Matsumoto Conflict with: Employed by Tsumura & CO., H. Kanno Conflict with: Employed by Tsumura & CO., M. Zushi Conflict with: Employed by Tsumura & CO., M. Yamamoto Conflict with: Employed by Tsumura & CO., H. Kuroki Conflict with: Financial interests from Tsumura & CO. relevant to this research, S. Nabeshima Conflict with: Financial interests from Tsumura & CO. relevant to this research., A. Yachie Conflict with: Financial interests from Tsumura & CO. relevant to this research, Y. Matsuoka Conflict with: Financial interests from Tsumura & CO. relevant to this research, H. Kitano Conflict with: Financial interests from Tsumura & CO. relevant to this research

Profiling of patient plasma exosomes to predict melanoma relapses

Martin Eberhardt[* 1], Jung-Hyun Lee[2], Katja Blume[1], Lisa Walter[3], Andreas Baur[1], Julio Vera[1]
[1]Department of Dermatology, UNIVERSITÄTSKLINIKUM ERLANGEN AND FRIEDRICH-ALEXANDER UNIVERSITY ERLANGEN-NÜRNBERG, Erlangen, Germany, [2]Department of Microbiology, The University of Chicago, Chicago, United States, [3]Central Institute of Medical Engineering, Friedrich-Alexander University Erlangen-Nürnberg, Erlangen, Germany

Secondary topic : Multi-omics

Your abstract : In the diagnosis of melanoma, blood-borne markers like S100B have been employed for decades. Patients who have been treated for melanoma are monitored regularly to detect relapses, i.e. secondary tumors that develop from the patient's minimal residual disease (MRD). Here, we report initial results from high-throughput plasma profiling of patient extracellular vesicles (exosomes) with the goal of predicting when these relapses will occur. We investigate two target molecule classes, miRNAs and extracellular protein ligands like cytokines and chemokines.

Our results show that the clinical stratification of melanoma patients is reproduced in the exosome profiles, with certain markers like IFN-γ being associated with controlled MRD and others like MCP-1 (CCL22) with progressing relapse. By combining the analysis of exosome measurements from a longitudinal patient cohort with clinical data, we will develop a predictive model of melanoma relapse. In contrast, miRNA measurements faced low signal-to-noise ratios and technical problems, posing the question whether miRNA signals from plasma exosomes can be picked up reliably with high-throughput technologies.

Disclosure of Interest: None Declared

A robust age-prediction model based on methylation data from multiple tissues

Koji Ishiya[*1], Sachiyo Aburatani[1]
[1]COMPUTATIONAL BIO BIG-DATA OPEN INNOVATION LABORATORY, NATIONAL INSTITUTE OF ADVANCED INDUSTRIAL SCIENCE AND TECHNOLOGY (AIST), Tokyo, Japan

Secondary topic : Multi-omics

Your abstract : The elucidation of individual characteristics from various types of biological data is an important theme in the field of clinical research. In fact, the accumulation of various types of genetic data from biological fields, such as genomic sequencing, gene expression, genotypes, and phenotypes, have exponentially increased. However, suitable methods for the elucidation of individual characteristics from such accumulated data have not been developed. In the present study, we focused on genome-wide methylation patterns in multiple tissues to elucidate one characteristic—age. The recognition of DNA methylation patterns is important for the understanding of epigenetics, and human DNA methylation analysis has been practically applied not only in research but also in clinical cases. The elucidation of age in cultured cells is important for the verification of experimental conditions, and methylation patterns in cancer tissues are also being studied for medical research. In forensics, age-prediction methods based on machine learning, such as neural networks, have been explored for the identification of unknown-age samples. Unfortunately, epigenetic clock errors between multiple tissues may occur because of differences in the methylation levels between various types of tissues. Some previous age-prediction models require several CpG methylation sites from genome-wide methylation arrays or bisulfite sequencing to minimize such errors. However, genome-wide methylation analysis for robust age prediction is not cost-effective because not all methylation sites are highly associated with age. Therefore, some technical and cost challenges in the estimation of age based on methylation data remain. Methylation data on more than 10,000 samples are available on well-managed databases, such as NCBI GEO, Encode Project, and NCI's Genomic Data Commons. In the present study, we built a robust age-prediction model using methylation patterns from multiple tissues that are available on well-managed databases. We combined appropriate data preprocessing with sparse regression to select informative methylation sites for the estimation of age. Our approach may provide opportunities for a fast, cost-effective, and robust estimation of age in the forensic or medical fields. In our poster presentation, we will introduce an optimized pre-processing approach for multi-tissue methylation data and the age-prediction model developed on the basis of these pre-processed datasets.

Disclosure of Interest: None Declared

Quantitative simulations predict treatment strategies against fungal infections in virtual neutropenic patients

Sandra Timme[*] [1, 2], Teresa Lehnert[1, 3], Maria T. E. Praußе[1, 2], Kerstin Hünniger[4, 5], Ines Leonhardt[3, 5], Oliver Kurzai[3, 4, 5], Marc Thilo Figge[1, 2, 3]

[1]Applied Systems Biology, LEIBNIZ INSTITUTE FOR NATURAL PRODUCT RESEARCH AND INFECTION BIOLOGY - HANS KNÖLL INSTITUTE, [2]Faculty of Biological Sciences, Friedrich Schiller University Jena, [3]Center for Sepsis Control and Care (CSCC) , Jena University Hospital, Jena, [4]Institute for Hygiene and Microbiology, University of Würzburg, Würzburg, [5]Fungal Septomics, Septomics Research Center, Friedrich Schiller University and Leibniz Institute for Natural Product Research and Infection Biology - Hans Knöll Institute, Jena, Germany

Secondary topic : Multiscale Systems Biology

Your abstract : The immune system protects the healthy status of the human body against various environmental threats, like viral, bacterial and fungal invaders. However, inborn or acquired diseases as well as medical treatments may impair its protective function. For example, neutropenia - a neutrophil deficiency - is associated with an increased risk for bacterial and fungal infections. Hence, it is of high importance to understand the interaction of immune cells and pathogens in health and disease. We here apply a systems biology approach that incorporates complementary wet-lab and dry-lab techniques.

We performed human whole-blood infection assays, where blood from healthy donors was infected with different pathogens. Subsequently, phagocytosis and killing was measured at several time points [1]. Based on these data, we developed a bottom-up virtual infection model using state-based and agent-based modeling for quantification of immune reaction rates and immune cell migration [2]. Simulations of immune dysregulation revealed that neutrophil paralysis resembles the infection outcome in neutropenic patients. Thus, we hypothesize that an improved neutrophil activity in terms of phagocytosis and migration might recover the infection outcome in neutropenic patients.

In our current study, we address this hypothesis by applying the bottom-up modeling approach [3]. First, we investigated the interaction of innate immune cells, like monocytes and neutrophils, with the two fungal pathogens *Candida albicans* and *Candida glabrata* under healthy immune conditions and subsequently studied the infection outcome in virtual neutropenic patients (VNP). Finally, we applied an *in silico* cytokine treatment to increase neutrophil activity. Our analyses predict that fungal infections in VNP can be successfully cleared by cytokine treatment of the remaining neutrophils and that this treatment will be more efficient for *C. glabrata* compared to *C. albicans* infection.

[1] Hünniger K. and Lehnert T. *et al.* (2014) A virtual infection model quantifies innate effector mechanisms and *Candida albicans* immune escape in human blood. *PLoS Comput Biol* 10(2):e1003479.

[2] Lehnert T. and Timme S. *et al.* (2015) Bottom-up modeling approach for the quantitative estimation of parameters in pathogen-host interactions. *Front Microbiol* 6(608).

[3] Timme S. *et al.* (2018) Quantitative simulations predict treatment strategies against fungal infections in virtual neutropenic patients. *Front Immunol* 9, 667.

Disclosure of Interest: None Declared

System medicine approaches identify PRKDC, ZEB2 and VSTM1 as transcriptional biomarkers discerning septic shock from SIRS in circulating granulocytes

Sonia Y. Velásquez[1], Tzu Ting Wei[1], Xiaonan Zhang[1], Jutta Schulte[1], Carsten Sticht[2], Anna Coulibaly[1], Holger A. Lindner[1], Ana Sofia Figueiredo[* 1]

[1]Department of Anesthesiology and Surgical Intensive Care Medicine, [2]Medical Research Center, Medical Faculty Mannheim, Ruprecht Karls University Heidelberg, Mannheim, Germany

Secondary topic : Systems Medicine

Your abstract : Sepsis and septic shock are the major cause of death in the Intensive Care Unit. Sepsis has been classically defined as a systemic inflammatory response syndrome (SIRS) triggered by an infection. As a response to infection, granulocytes enter circulation and phagocytize pathogens. Timely diagnosis of sepsis is live saving but the distinction between sepsis and SIRS remains a medical challenge. Here, we use systems medicine approaches to identify the transcriptional biomarkers that differentiate between septic shock and SIRS, as well as the underlying mechanisms that regulate the expression of these genes. We analyzed microarray data of granulocytes isolated from blood of patients with septic shock, SIRS and those undergoing pre-surgery examination to identify the biomarkers specific for infection and not inflammation in septic shock. We validated these results in the primary and in an independent cohort by RT-PCR and the branched DNA method. Results indicate that *PRKDC, ZEB2*, *and VSTM1* distinguish between septic shock and SIRS. We further used these results to model potential molecular mechanisms these genes are involved in. These comprise both pro-inflammatory and anti-inflammatory pathways that are potentially activated in septic shock. We propose that these pathways have an antagonist effect at the functional level. Specifically, that the pro-inflammatory response activates ROS production and cell survival via the signaling cascade PI3K-AKT, while the anti-inflammatory response represses ROS production and induces apoptosis via signaling networks downstream of the receptor *VSTM1*. Moreover, AKT and DNA-PKc (the protein encoded by *PRKDC*), form a complex where AKT phosphorylates DNA-PKc and this kinase, in turn, phosphorylates itself. While part of this complex, DNA-PKc is an essential player in DNA repair of double strand breaks, with the ability to trigger a host innate immune response to infection. While the mechanisms that control the expression of *PRKDC* are still elusive, ZEB2 is a transcription factor that can bind to the promoter region of that gene. Our results reveal a novel set of biomarkers of septic shock and propose specific molecular differential mechanisms in septic shock vs. SIRS. This paves the way not only for the improved diagnosis of sepsis, but also for the discovery of new drug targets to fight this systemic disease.

Disclosure of Interest: None Declared

Mathematical modeling of the energy metabolism of neuroblastoma cells

Mareike Simon[*1], Uwe Benary[1], Britta Tjaden[2], Alexander Schramm[2], Jana Wolf[1]
[1]Mathematical Modelling of Cellular Processes, Max Delbrück Center for Molecular Medicine in the Helmholtz Association, Berlin, [2]Department of Medical Oncology, West German Cancer Center, University Hospital Essen, University of Duisburg-Essen, Essen, Germany

Secondary topic : Modelling Networks and Circuits

Your abstract : Alterations in the metabolism of cancer cells have been first identified by Otto Warburg in the 1920s, when he discovered that cancerous cells take up more glucose and produce more lactate than non-cancerous cells, an effect now known as Warburg effect or aerobic glycolysis. In the last years additional alterations were identified and a deregulated energy metabolism is now recognized as a hallmark of cancer.
We are especially interested in metabolic alterations in the pediatric cancer neuroblastoma. Neuroblastoma is one of the most common cancers in children, accounting for approximately 15% of cancer death in children. A main prognostic factor is the amplification of the MYCN oncogene, a transcription factor of the MYC family. The overall survival of patients with tumor-specific MYCN amplification is significantly worse than that of those without MYCN amplification. It has been shown that MYCN upregulates the expression of glycolytic enzymes, which could promote the Warburg effect.
We investigate the impact of MYCN on the energy metabolism in the framework of ordinary differential equation (ODE) based modeling. A detailed model of the glycolysis is developed and fitted to experimental data. The model will be able to represent the energy metabolism under different nutrient conditions. Sensitivity analysis will be applied to investigate the influence of the model parameters in order to identify possible drug targets.

Disclosure of Interest: None Declared

Synthesis of liposome-polymeric nanoparticle hybrid systems for therapeutic applications

Ozlem Ozbek* [1], Kutlu O.Ulgen[1], Nazar Ileri Ercan[1]
[1]Chemical Engineering, BOGAZICI UNIVERSITY, Istanbul, Turkey

Your abstract : Nanoparticles, which have been used in drug targeting processes, are polymeric colloidal structures. The types of nanoparticles are mainly divided into two categories: inorganic, such a silica, graphene, iron oxide and organic such as polymers, micelles, liposomes. The capability of producing the nanoparticles at different sizes, morphologies and surface properties makes them promising materials to deliver specific compounds to the cells. Liposomes are closed vesicles consisting of phospholipid bilayers. They are non-toxic, biodegradable, biocompatible and can incorporate both hydrophilic and hydrophobic substances. But, there is a possibility of leakage of the encapsulated substances because of mechanical instability of bare liposomes. The design and synthesis of liposome-nanoparticle hybrid systems get great attention to improve physicochemical properties of both agents [1-4]. The liposome-nanoparticle hybrid systems improve the drug loading capacity and mechanical stability and offers controlled morphology and narrow size distribution [5]. In the present study, polystyrene latex nanoparticles were encapsulated by liposomes, which were synthesized from phospholipid DOPC (1,2-Dioleoyl-sn-glycero-3-phosphocholine). Moreover, the toxicity and the uptake of hybrid nanoparticles were investigated in the model organism, *Saccharomyces cerevisiae*. The viability of the yeast cells after hybrid nanoparticle exposure determined by CFU (Colony Forming Unit) method and microscopic visualization presents promising results for therapeutic applications.

References:

[1] C. Cordon, M. Piva, C. Melo, M. Pinhal, and E. R. Suarez, “Nanoparticles as platforms of molecular delivery in diagnosis and therapy,” *OA Cancer*, vol. 1, Dec. 2013.
[2] S. Mura, J. Nicolas, and P. Couvreur, “Stimuli-responsive nanocarriers for drug delivery,” *Nat. Mater.*, vol. 12, p. 991, Oct. 2013.
[3] M. Mathiyazhakan, C. Wiraja, and C. Xu, “A Concise Review of Gold Nanoparticles-Based Photo-Responsive Liposomes for Controlled Drug Delivery,” *Nano-Micro Lett.*, vol. 10, no. 1, p. 10, 2017.
[4] S. Haque and E. Chowdhury, “Recent Progress in Delivery of Therapeutic and Imaging Agents Utilizing Organic-Inorganic Hybrid Nanoparticles,” *Curr. Drug Deliv.*, vol. 14, Nov. 2017.
[5] V. Colapicchioni *et al.*, “Killing cancer cells using nanotechnology: novel poly(I:C) loaded liposome-silica hybrid nanoparticles,” *J. Mater. Chem. B*, vol. 3, no. 37, pp. 7408–7416, 2015.

Disclosure of Interest: None Declared

The influence of EGF/HGF receptor abundance on efficacy of targeted therapy in NSCLC cell lines

Florian Salopiata[*1], Helge Hass[2], Siegfried Hänselmann[3], Yu Qiang[4], Marc Schneider[5], Michael Meister[5], Andreas Raue[6], Karl Rohr[4], Dirk-Peter Herten[3], Marcel Schilling[1], Jens Timmer[2], Ursula Klingmüller[1]

[1]Division of Systems Biology of Signal Transduction, German Cancer Research Center (DKFZ), Heidelberg, [2]Centre for Systems Biology, University of Freiburg, Freiburg, [3]Cellnetworks Cluster and Institute of Physical Chemistry, [4]Bioinformatics and Functional Genomics, Heidelberg University, [5]Translational Research Unit, Thoraxklinik at University Hospital Heidelberg, Heidelberg, Germany, [6]Merrimack Pharmaceuticals, Inc., Boston, United States

Your abstract : Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related deaths worldwide. Unfortunately, the currently available targeted therapies such as epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) treatment lead to only a few months increased survival due to the development of therapy resistance. It is suspected that this resistance can be mediated by the crosstalk of EGF and hepatocyte growth factor (HGF) induced signal transduction. Yet, the underlying mechanisms remain unknown.

In this study time resolved quantitative data for EGF and HGF induced signal transduction was acquired in NSCLC cell lines. A set of NSCLC cell lines was examined that harbor different mutations in the EGFR and differ in their expression levels of EGFR and HGF receptor (MET). The experiments showed a cell type-specific enhanced activation of MET phosphorylation upon co-stimulation with EGF and HGF. To gain insights into mechanisms regulating the interaction of the receptors, the dynamic signaling data was utilized to develop a mechanistic pathway model. Applying this mathematical model, we predicted that the association of EGFR and MET is stoichiometry dependent leading to a prolonged half-life of the MET receptor. We hypothesized that the increased stability of MET in cells with high EGFR to MET expression ratio causes the observed enhanced MET activation. This was validated by changing the receptor stoichiometry using retroviral transduction, siRNA in the cell lines and by screening nine other NSCLC cell lines with distinct EGFR and MET expression ratios. Further, our model suggested an impact of the EGFR and MET expression levels on TKI efficiency. With this strategy we propose a novel approach to develop strategies to avoid the emergence of therapy resistance depending on the relative receptor abundance and suggest new combinational therapies to improve response rates of lung cancer patients.

Disclosure of Interest: None Declared

The adult neurogenesis map

Rupert Overall[*1]
[1]GERMAN CENTER FOR NEURODEGENERATIVE DISEASES (DZNE), Dresden, Germany

Your abstract : The hippocampus is a key brain structure for learning and memory. It not only processes input from the environment, but also fundamentally influences behaviour. This means that the neural network in the hippocampus is a core part of an information loop connecting environmental stimulus and response. It is particularly intriguing that this special brain region is also home to a population of neural stem cells which allow the environmentally-regulated creation of new neurons, throughout the life of the organism, that add an extra level of flexibility to hippocampal performance. We have previously shown that the regulation of the stem cell pool and the generation of new neurons are under complex genetic control. We also maintain a structured database of all genes reported to affect adult hippocampal neurogenesis in some way. We are now extending this effort to encompass behavioural phenotypes and environmental stimuli. The resulting information is being organised into a structured SBML map to enable interactive browsing and complex searching of the knowledgebase, as well as to provide a platform for predictive modelling. We present here an outline and working draft of the Adult Neurogenesis Map and look forward to community feedback as the project expands.

Disclosure of Interest: None Declared

Systems biology model of the mucosal immune system in the context of inflammatory bowel disease

Sabine Stübler[*1,2], Charlotte Kloft[3], Wilhelm Huisinga[1]
[1]Mathematical Modelling and Systems Biology, Institute of Mathematics, UNIVERSITY OF POTSDAM, Potsdam, [2]PharMetrX Graduate Research Training Program, Berlin/Potsdam, [3]Institute of Pharmacy, Freie Universität Berlin, Berlin, Germany

Your abstract : Inflammatory bowel disease (IBD, major forms: Crohn's disease and Ulcerative colitis), is a chronic disease caused by autoimmunity of T cells against commensal bacteria in the gut. Current treatment regimens include corticosteroids, immunomodulatory small molecule drugs and monoclonal antibodies targeting TNF-a, but the therapeutic outcome differs highly between patients. A better understanding of the mucosal immune system in the context of IBD is therefore highly desirable. The objective of this work was to mathematically describe the cellular processes of the intestinal immune system to provide a basis for further analysis of drug effects and inter-individual variability in response.

We identified important processes of the mucosal immune system (innate and adaptive) on the cellular level through an extensive literature research. These processes were described (i) in terms of parameter values from literature, (ii) by estimating parameters from literature data from human, mouse or in vitro studies, or (iii) by assuming reasonable parameter ranges resulting in adequate model behaviour, if literature data were not available. We combined these processes into a systems biology model that described concentrations of several cell types in the gut lamina propria and the mesenteric lymph nodes.

The developed ODE model included dendritic cells, T cells (naive, memory, helper and regulatory), macrophages, neutrophils and bacterial cells. Simulations were able to reflect the main characteristics of the mucosal immune system: Bacteria up to a threshold concentration were efficiently cleared in the model. As first line of defence neutrophils infiltrated the lamina propria, dendritic cells and macrophages followed. Dendritic cells and macrophages shifted to an inflammatory state upon activation and recovered when the bacteria were eliminated. Effector T cell concentrations increased with a delay. After the acute inflammation all cell concentrations returned to baseline. The next steps will be to include IBD triggers, pharmacokinetics and drug effects, and to generate a virtual population of patients to analyse inter-individual variability.

The developed systems biology model was able to reflect the main characteristics of the mucosal immune system. This is a promising first step towards modelling the pathological processes and drug effects in IBD.

Disclosure of Interest: None Declared

Investigating the association of two genetic risk scores with anthropometry, insulin sensitivity and MRI derived fat distribution

Francesca Frau[* 1], Andrianos Yiorkas[2], Andrea Mari[3], Naeimeh Atabaki-Pasdar[4], E Louise Thomas[5], Wareed Alenaini[6], Hanieh Yaghootkar[7], Alex Blakemore[2], Timothy M Frayling[7], Hartmut Ruetten[8], Leen 't Hart[9], Paul W Franks[4], Karla V Allebrandt[1], Jimmy D Bell[6], Ewan Pearson[10]

[1]TMED Translational Informatics, Sanofi, Frankfurt am Main, Germany, [2]Section of Investigative Medicine, Imperial College London, London, United Kingdom, [3]Institute of Neuroscience, National Research Council,, Padua, Italy, [4]Department of Clinical Sciences, Genetic and Molecular Epidemiology Unit, Lund University, Malmö, Sweden, [5]Research Centre for Optimal Health, University of Westminster, London, [6]Research Centre for Optimal Health, University of Westminster, London, [7]Genetics of Complex Traits, University of Exeter Medical School, Exeter, United Kingdom, [8]Translational Medicine and Clinical Pharmacology, Sanofi, Frankfurt am Main, Germany, [9]Dept. of Molecular Cell Biology and Section Molecular Epidemiology, Leiden University Medical Center, Leiden, Netherlands, [10]Division of Molecular and Clinical Medicine, School of Medicine, University of Dundee, Dundee, United Kingdom

Your abstract : Background and aims: A genetic risk score (GRS) composed of 11 SNPs is associated with fasting insulin but lower adiposity. Previous studies showed that this GRS is associated with low HDL-cholesterol, low adiponectin, raised triglycerides and ALT despite higher BMI.

This apparent paradox is likely explained by increased visceral s/c fat ratio and CT-determined liver fat measured by different consortia.

A further study has expanded the cluster of 11 SNPs (11-SNPs) to 53 SNPs (53-SNPs) that were concordant for 3 phenotypes of increased fasting insulin adjusted for BMI, decreased HDL-cholesterol and increased triglycerides.

To understand better the genetic factors involved in body fat distribution we evaluated the association of these genetic risk scores with anthropometric, glycaemic and MRI phenotypes and we performed a meta-analysis using data from IMI-DIRECT pre-diabetic, IMI-DIRECT diabetic and the UK Biobank (UKBB) studies.

Materials and methods: IMI-DIRECT subjects were recruited into a longitudinal study of glycaemic deterioration; UKBB subjects were selected from a dataset of over 500,000 individuals. A linear regression analysis was performed (using sex, age, age2, centre, BMI and ancestry principal components as covariates) to assess the association between the genetic risk scores and the outcomes. These outcomes included MRI based measures of liver, pancreatic, subcutaneous, and visceral adiposity. A meta-analysis of the results and an analysis stratified by sex were performed.

Results: The 11-SNPs GSR was associated with lower BMI (beta=-0.045, p=0.004), lower WHR (beta=-0.003, p=0.015) and lower waist circumference (beta=-0.04, p=0.007) in men. Moreover, it was associated with a decrease of hip circumference (beta=-0.033, p=0.037) and with higher liver fat (total: beta=0.062, $p=1.0x10^{-4}$) in both sex subgroups.

The meta-analysis of the 53-SNPS GSR results showed a significant association with lower BMI, lower WHR, and lower hip circumference (BMI: beta=-0.058, $p=3.0x10^{-4}$; WHR: beta=-0.039, p=0.003; hip circumference: beta=-0.062, $p=1.0x10^{-4}$) in men. Moreover, it was associated with a decrease of waist circumference in the total group (beta=-0.064, $p=1.8x10^{-5}$) and in both sex subgroups.

The 53-SNPs GRS was not as strongly associated with higher liver fat as the 11-SNPs GSR.

Conclusions: Common human alleles associated with insulin resistance are also associated with MRI based measures of liver fat accumulation despite associations with higher BMI.

Disclosure of Interest: F. Frau Conflict with: Sanofi employee, A. Yiorkas: None Declared, A. Mari: None Declared, N. Atabaki-Pasdar: None Declared, E. L. Thomas: None Declared, W. Alenaini: None Declared, H. Yaghootkar: None Declared, A. Blakemore: None Declared, T. M. Frayling: None Declared, H. Ruetten Conflict with: Sanofi employee, L. 't Hart: None Declared, P. W. Franks: None Declared, K. V. Allebrandt Conflict with: Sanofi employee, J. D. Bell: None Declared, E. Pearson: None Declared

Mathematical model of tumor immune interaction in chronic myeloid leukemia: application to treatment cessation

Thomas Lepoutre[*1]
[1]INRIA, villeurbanne, France

Your abstract : Chronic myeloid leukemia (CML) is a myeloproliferative disorder caused by the BCR-ABL fusion oncogene, which encodes for a constitutively active tyrosine kinase. This cancer represents one of the greatest success of the targeted therapies, Tyrosine kinase inhibitors (TKIs), that brings the life expectancy of patients close to healthy patients. The current objective is to pass from a paradigm of life long treatment (with the associated side effects and cost issues) to time-limited therapy. It appears indeed that some patients can stop treatment without relapsing. However, this treatment cessation might correspond to controlling the disease and not to its eradication. There are many indications that the autologous immune response plays a key role in modulating the response to TKIs and its quality. In this work we consider a model of tumor immune interaction. On of the main consequence of the model is that treatment cessation success is interpreted as a successful control of the disease rather than an eradication of the disease. It provides moreover to predicitions that have been recently backed up by indenpendent clinical trials namely that after a first phase of decline, dose reduction is safe and that deescalation shall be prefered to immediate cessation.

Disclosure of Interest: None Declared

Temporal comorbidity analysis of disease trajectories using semantic, genetic and phenotypic similarities: an application to prostate cancer

Alexia Giannoula[*1], Emilio Centeno[2], Ferran Sanz[1], Laura Furlong[1]
[1]Dept of Experimental and Health Sciences, UNIVERSIDAD POMPEU FABRA, BARCELONA, SPAIN, [2]Medical Research Institute of the Hospital del Mar, Medical Research Institute of the Hospital del Mar, Barcelona, Spain

Secondary topic : Methodological developments for Systems Biology

Your abstract : Prostate cancer is the most common type of neoplasm diagnosed in men and the third most frequent cause of cancer death in Europe, thereby constituting a substantial public health burden. One of the most critical problems that prostate cancer patients and their physicians face is uncertainty in deciding about screening and treatment. Central to clinical decision making is the presence of comorbidities, as the treatment for prostate cancer may exacerbate comorbid diseases and inversely, certain comorbid diseases may negatively affect the outcome of the treatment. A deeper understanding of the role of comorbidities in men with prostate cancer is important for the optimal disease management and patients' survival. The time factor, although typically ignored so far, is crucial in the assessment of comorbidities, as it permits to identify complex disease associations and study disease progression. This work aims at performing a large-scale population-based comorbidity study on prostate cancer patients within an epidemiological, molecular and phenotypic context, by taking the time factor into account. The clinical histories of 21,309 hospitalized prostate cancer patients are extracted from a Catalonian Electronic Health Record and shared disease trajectories of variable lengths are identified. Subsequently, an unsupervised clustering algorithm is applied, based on Dynamic Time Warping (DTW), that groups trajectories together according to temporal characteristics that they share and irrespectively of their number of diagnoses, duration and time scale. Three distance metrics are proposed to be used in the DTW algorithm for measuring disease similarities : i) a semantic similarity distance metric based on the Unified Medical Language System topology, ii) a genetic similarity metric through the use of a Jaccard index on the associated shared-gene sets and iii) a phenotypic similarity one that uses the Human Phenotype Ontology. More than 2,000 prostate-cancer shared disease trajectories were identified, of which three different clustering configurations were obtained, based on the three aforementioned disease similarity metrics. Complex time-dependent disease patterns were identified in prostate-cancer trajectories, according to semantic, genetic and phenotypic characteristics, thereby enabling a better understanding of the associated comorbidities within a temporal context that could serve as the basis of a preliminary disease prediction system.

Disclosure of Interest: None Declared

Identification of a novel target for senotherapeutics in fibroblasts

Sugyun An[*1], Junsoo Kang[1], Soobeom Lee[1], Kwang-Hyun Cho[1]
[1]Department of Bio and Brain Engineering, KAIST, Daejeon, Korea, South

Secondary topic : Modelling Networks and Circuits

Your abstract : Identification of a novel target for senotherapeutics in fibroblasts

Junsoo Kang, Sugyun An, Soobeom Lee, Kwang-Hyun Cho[*]
Laboratory for Systems Biology and Bio-inspired Engineering, Department of Bio and Brain Engineering, Korea Advanced Institute of Science and Technology (KAIST), Daejeon, 34141, Republic of Korea

Cellular senescence, an irreversible cell cycle arrest, plays an important role in aging which is a major risk factor for many diseases including cancer. So, senotherapeutics that specifically target senescent cells have been under active investigation. However, previous studies showed that treating senescent cells without a systemic understanding of cellular senescence can cause side effects such as cancer initiation. To resolve this problem, we have constructed Boolean network models based on literature and reverse phase protein array (RPPA) data from fibroblasts using evolutionary algorithm for optimization of the discrete logic. From our model simulations, we found a promising target for senotherapeutics. Target inhibition experiments also confirmed that target inhibition in fibroblasts not only prevents cellular senescence but also reverses senescent cells to quiescent cells. Furthermore, we demonstrated that fibroblasts reversed by target inhibition show controlled proliferation when proliferation signals are given. In conclusion, using a systems biology approach, we identify a novel target for senotherapeutics in fibroblasts.

Acknowledgements:
This work was supported by the KAIST Future Systems Healthcare Project from the Ministry of Science and ICT, and the National Research Foundation of Korea (NRF) grants funded by the Korea Government, the Ministry of Science and ICT (2017R1A2A1A17069642 and 2015M3A9A7067220).

[*]Corresponding author, E-mail: ckh@kaist.ac.kr, Phone: +82-42-350-4325, Fax: +82-42-350-4310, Web address: http://sbie.kaist.ac.kr.

Disclosure of Interest: None Declared

Multi-affinity ligand systems may confer evolutionary advantage: a case study in interferon

Arran Hodgkinson[*1], Gilles Uzé[1], Ovidiu Radulescu[2]
[1]Biological Physics & Systems Biology, [2]Dynamiques des Interactions Membranaires Normales et Pathologiques, Université de Montpellier, Montpellier, France

Secondary topic : Modelling Networks and Circuits

Your abstract : Many biological systems contain several ligands of varying affinities to the same receptor; an example of which is the system of the cytokine interferon (IFN). The presence of the pathogen initiates the production of IFNβ (1st wave response) who will bind the IFN receptors IFNAR1 and IFNAR2 and, in the continued presence of this pathogen, may activate a feedback loop for the production of all 13 human type I IFN species (2nd wave response). The impact of the existence of both high (IFNβ) and low (IFNα) affinity IFNs, however, remains unresolved in mechanistic biology.

In order to establish the roles that each of these IFN strains play, we produce a mathematical model containing cells that produce IFNα, IFNβ, or both proteins. To do so, we employ a novel framework that combines reaction-diffusion and Liouville equations in order to compute time dependent distributions of cells in multiple dimensions; spatial and internal, metabolic state dimensions. We particularised this system for the IFN producer model, focussing on the binding dynamics of high and low affinity ligands to the IFNAR1/2 receptors; activation of the Jak-STAT upon the binding of these receptors; and the consequent transcription of IFN stimulated genes (ISGs), in a spatial context.

Cells who could only produce IFNβ were able to sustain their own activity whilst those who were capable of producing only IFNα showed an ability to communicate the IFN signal to distant clusters, potentiating their metabolic state. Cells capable of producing both IFNs were able to sustain their own activity and activate distant clusters, with low affinity ligands increasing the rapidity with which cells entered the 2nd wave response. To asses the evolutionary benefit of low affinity ligands to the host, we simulated a system with 1 high, 10 medium, and 2 low affinity ligands, such as in humans. We found that spatial pathogenic diffusivity was important to the impact of each ligand and that systems with the additional low affinity ligands, compared to those without, achieved up to a ∼25% reduction in pathogenic load.

Numerical results suggest that IFNβ plays a major role in consolidating and IFNα in propagating, in advance of a diffusing pathogen, a locally induced IFNβ signal. This new framework, and its ability to simulate complex dynamical systems, describes an advantage to having a system of ligands with multiple affinities may confer an augmented ability to rid the host of a pathogen and an evolutionary advantage.

Disclosure of Interest: None Declared