Developmental Systems Biology A
SUNDAY, OCTOBER 28 – 04:00 PM – 05:40 PM

Coordination of different stem cell niches during homeostatic growth of the adult fish eye

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Your abstract : The long-held notion that adult stem cells deterministically undergo self-renewing asymmetric divisions was recently upturned in favor of a neutral drift model where individual cells behave stochastically and self-renewal happens at the level of the cell population. While this model holds true for tissues in homeostatic turnover such as most adult mammalian tissues, tissues with adult homeostatic growth such as the neural retina of the fish eye challenge the pure neutral drift model.
Here we combine *in vivo* and *in silico* clonal lineage tracing in the neural retina and retinal pigmented epithelium of the eye of medaka fish (*Oryzias latipes*) to address the impact of stochastic behavior in two independent stem cell niches in the same organ. Using a 3D cell-centre agent-based paradigm, we distil the system to its minimal components, and use this model as a virtual playground to explore hypotheses about fundamental growth modes of the system.
Our simulation predicts that stem- and progenitor cell fates as well as the spatial segregation of stem- and progenitor domains are emergent properties, as the topology of the niche preconditions the system to undergo a spatially biased stochastic neutral drift. Further, our analyses revealed that stem cells in the neural retina behave less stochastically than predicted by a purely random model, but more stochastically than a purely deterministic model. By controlling their division axis, stem cells in the neural retina direct growth and shape the organ, whereas stem cells for the retinal pigmented epithelium display greater stochasticity and follow external instructive signals. Thus, we show how different tissues in one organ adapt their proliferation strategies to synchronize their growth. These strategies manifest in the quantifiable levels of stochasticity of macroscopic cell behavior.
Our work highlights how a minimal target node for evolution – the proliferation of neuroretinal stem cells – can be exploited to adapt whole-organ morphogenesis in a complex vertebrate organ.

Disclosure of Interest: None Declared

OCT4 is required at the M-G1 transition to reestablish chromatin accessibility at enhancers in pluripotent stem cells

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Secondary topic : Multi-omics

Your abstract : Fast-cycling pluripotent stem cells maintain cell identity through indefinite cell divisions. During mitosis, transcription stops and most proteins are evicted from chromatin. This raises the question of how transcriptional programs are reactivated following division. Some histone marks are maintained in mitosis and a subset of transcription factors including the central pluripotency regulators OCT4 and SOX2 remain bound to the mitotic genome. We and others have shown that degradation of OCT4 and SOX2 specifically at the M-G1 transition hampers pluripotency maintenance, abrogates the differentiation-inducing ability of SOX2, and decreases the reprogramming efficiency of OCT4, suggesting that mitotic binding is required for their action on cell fate.

To understand if OCT4 is involved in reactivating ES cell regulatory elements upon mitotic exit, we degraded OCT4 at the M-G1 transition and compared chromatin accessibility in the following cell cycle to cells where OCT4 was always present. Mitotic degradation of OCT4 decreased chromatin accessibility at roughly half of all OCT4-bound loci, which were strongly enriched for enhancers. Some of these loci recovered to control-levels by late G1, while others remained differentially accessible even toward the end of the cell cycle when OCT4 levels had been restored for several hours. Notably, these highly affected loci are enriched for OCT4 and SOX2 mitotic binding events and include ES cell super-enhancers. We hypothesize that OCT4 genomic occupancy at the M-G1 transition serves to reestablish accessibility at ES cell enhancers and that failure to do so has prolonged effects that result in pluripotency loss. We now aim to elucidate how this impaired accessibility affects downstream events such as co-factor binding and transcription as well as to determine the role of SOX2 in maintaining chromatin accessibility after mitosis.

Disclosure of Interest: None Declared

Mitotic chromosome binding predicts transcription factor dynamics, target site occupancy and ability to modify chromatin accessibility

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Your abstract : Mammalian transcription factors (TFs) differ in dynamic properties such as nuclear mobility, specific/non-specific DNA binding affinity for open/closed chromatin, and ability to open condensed chromatin. How these properties are related and whether they confer differential ability of TFs to occupy their genomic targets is unknown. To address these questions, we combined live cell quantitative measurements of mitotic chromatin binding for 507 TFs, live cell/single molecule imaging of TF mobility and DNA binding, and genome-wide mapping of TF binding and chromatin accessibility. We show that mitotic binding of TFs is a strong predictor of both mitotic and interphase TF mobility, as well as sequestration into DNA-rich compartments in interphase. Strikingly, the fraction of TF molecules bound to mitotic chromosomes provides a strong prediction of TF occupancy at specific genomic locations in interphase ranging over three orders of magnitude. Mitotic chromosome binding was only weakly correlated to relative preference of TF binding to closed chromatin, but correlated with the ability of TFs to modify chromatin accessibility. Our work sheds light on the broad range of TF dynamics, localization, ability to interact with chromatin and to modify the epigenetic landscape.

Disclosure of Interest: None Declared

Modeling cell fate specification during early embryonic development in mouse

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Secondary topic : Modelling Networks and Circuits

Your abstract : During embryonic development, the specification of different cell fates results from interactions between transcription factors. These regulatory networks often exhibit multiple stable steady states (multistability), providing a common dynamical basis for differentiation. I will present here a model for early murine embryogenesis which describes the specification of cells from the inner cell mass (ICM) into epiblast (Epi) or primitive endoderm (PrE). The model incorporates the intracellular gene regulatory network as well as the intercellular interactions involving Erk/Fgf4 signaling pathway. It consists of a set of ordinary differential equations which are analyzed by means of numerical simulations and bifurcation diagrams. The network displays tristability in a range of Fgf4 concentrations, accounts for the self-organized specification process observed in vivo, and predicts that heterogeneities in extracellular Fgf4 concentration play a primary role in the spatial arrangement of the Epi/PrE cells in a salt-and-pepper pattern. A multiscale extension of the model accounting for cell division in the 3-dimensional space recapitulates a variety of in vivo observations on wild-type and mutant embryos and allows to study the effect of various treatments interfering with the Fgf signalling pathway. Simulations of this model suggest that initial cell-to-cell differences originating from slight inhomogeneities in extracellular Fgf4 signalling, possibly in combination with slightly different concentrations of the key transcription factors between daughter cells, are sufficient to trigger cell specification in a robust and reproducible manner.

Disclosure of Interest: None Declared

Noise-resistant developmental reproducibility in vertebrate somite formation

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Secondary topic : Modelling Networks and Circuits

Your abstract : Embryonic development is highly reproducible, although molecular processes at the single-cell level are intrinsically stochastic. How the multi-cellular system resists the inevitable noise to establish developmental reproducibility is a fundamental question in developmental biology. Toward this end, we focused on vertebrate somitogenesis as a representative system, because equal-sized somites are repeatedly reproduced within a single embryo whereas somite sizes become irregular in segmentation clock gene-deficient embryos. However, the effect of noise on developmental processes has not been fully investigated, because of the technical difficulty in identifying the noise source and manipulating the noise intensity in experiments. In this study, we investigated the mechanism of noise-resistant mechanism of somitogenesis using a combined approach of a mathematical model and live imaging in zebrafish embryo. The mathematical model described ERK-mediated somitogenesis, in which bistable ERK activity is regulated by an FGF gradient, cell-cell communication, and the segmentation clock, subject to the intrinsic noise. In the model simulation, the ERK activity in the presomitic mesoderm was distributed in a step-like gradient, and its boundary was posteriorly shifted by the clock in a stepwise manner, leading to regular somite formation. We showed that this somite regularity was robustly maintained against the noise. We experimentally confirmed the simulated stepwise shift of ERK activity by live imaging in zebrafish embryo with FRET-based biosensor of ERK. The model further predicted that removing the clock still generates the stepwise shift of the ERK activity, but at irregular timing with irregular distance owing to the noise, resulting in somite size variation. Through FRET imaging in clock-deficient embryo, we confirmed this model prediction. Through theoretical analysis, we clarified that the intrinsic noise induces spontaneous formation of irregular-sized somites in the absence of the clock, and that the clock plays an important role in suppressing the effect of inherent noise on noise-resistant reproducible somite formation.

Disclosure of Interest: None Declared

Multiscale Systems Biology
SUNDAY, OCTOBER 28 – 04:00 PM – 05:40 PM

Deciphering yeast physiology by a multi-scale framework integrating cell cycle and metabolism

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Secondary topic : Modelling Networks and Circuits

Your abstract : Cell division cycle and metabolism are coupled networks. Cell growth and division require synthesis of macromolecules which is dependent on metabolic cues. Conversely, metabolites involved in storage metabolism fluctuate periodically during cell cycle progression. High-throughput and mechanistic interactions are reported between these two networks, and computer models of cell cycle and metabolism are being developed. However, to date no effort has been made to explore how cell's physiology is regulated by the integration of these networks in any organism.
Here a multi-scale framework is presented that integrates a Boolean cell cycle model with a constraint-based model of metabolism in budding yeast, including mechanistic and high-throughput interactions. An evolutionary optimization algorithm has been developed to generate models that incorporate these interactions iteratively, to explore their directionality and effect. Model results are verified against metabolic pathway activity and enzyme concentrations. Through Boolean logic, activity of cell cycle nodes activates or inhibits metabolic reactions. Conversely, presence or absence of a metabolic flux promotes or prevents activity of cell cycle nodes, respectively.
First, seven known interactions in which cell cycle components regulate metabolic enzymes were used to integrate the two models. Implementing storage metabolites in the *in silico* framework resulted in the alignment of flux changes with enzyme concentration changes up to 50%, highlighting their importance for metabolic changes during the growth phase of the cell cycle. Subsequently, high-throughput set of interactions and 18 random sets of interactions were optimized by the evolutionary algorithm. The real set of interactions showed higher scores with respect to the proteomic data and a consistent interaction pattern. Through machine learning, relevant interactions between cell cycle and metabolism were identified, and design criteria of cell cycle-mediated metabolic regulation were predicted, with sulfur metabolism, oxidative phosphorylation and central carbon metabolism active or inactive in definite cell cycle phases.
The first multi-scale framework that integrates cell cycle and metabolism in budding yeast reveals marked changes in flux distributions through different cell cycle phases. This framework may be employed to capture the mechanistic basis of robustness of cell cycle networks, by highlighting metabolic causes of cell cycle arrest.

Disclosure of Interest: None Declared

Enabling the comparison of conventional and non-conventional winemaking Saccharomyces species with genome-scale models

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Secondary topic : Quantitative Systems Physiology
Your abstract : Saccharomyces cerevisiae is the predominant yeast in wine fermentations because of its high fermentative capacity and ethanol resistance. However, consumers demand less alcoholic wines with a more aromatic profile or with higher glycerol content; rendering this species less attractive for industrial wine production. Since current regulation limits the use of metabolic engineering strategies based on genomic interventions. Therefore recent works suggest the possibility of using non-conventional Saccharomyces species to start the winemaking process. However, the rational design of new fermentations using non-conventional Saccharomyces species requires an improved understanding of their physiological and metabolic idiosyncrasies along with models that can predict their performance.

Multi-Scale mathematical modeling of the process brings the possibility of understanding the evolution of yeast metabolism in a time-varying environment. For this purpose, kinetic models describe the dynamics of extracellular compounds while an iterative flux balance analysis allows for the dynamic description of intracellular metabolic fluxes.

In this work, we combine an experimental approach with genome-scale models to understand and to explain the physiological and metabolic differences among S. cerevisiae T73 and S. uvarum BMW58 during wine fermentations at high temperature (25 °C). Microvinification experiments, i.e. small-scale batch cultures, mimicking wine fermentations were carried out for both species and samples collected across the fermentation period. Samples were used to characterize the dynamics of yeast physiology (cell volume, OD600, biomass and number of colony forming units) and extracellular metabolism (49 metabolites measured by high-performance liquid chromatography). The data-set used to recover the kinetic parameters, includes the most relevant sugars, organic acids, aromas and amino-acids to fermentation and final wine composition. As for the model we use the newest YEAST 8 GEM.

The final models were able to reproduce the dynamics of growth and the most relevant metabolites. The combination of the experimental approach with the model highlighted relevant metabolic differences between species, namely, at the level of redox balance, amino acid metabolism and energetics. Our results reveal that S. uvarum is a good candidate to lead or (co-lead) fermentations seeking for increased production of aromatic compounds.

Disclosure of Interest: None Declared

A multiscale mathematical model of neural progenitor dynamics during the development of the cerebral cortex in mice

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Secondary topic : Multiscale Systems Biology

Your abstract : The multiple sensory, motor and cognitive functions of the mammalian cerebral cortex are supported by a diversity of neuronal subtypes. The formation of this complex structure during brain development requires producing the correct number and subtypes of neurons at the proper position. Neurogenesis - the generation of new neurons from progenitors cells - in the cerebral cortex of mice involves the coordinated divisions of two main types of progenitor cells, whose numbers, proliferation modes and cell cycle durations set up the final neuronal output. To understand the respective roles of these factors in neurogenesis, we combine experimental in vivo studies with mathematical modeling and numerical simulation of the dynamics of neural progenitors. Our model takes into account the dividing apical progenitors (AP) engaged into neurogenesis, both neurogenic and proliferative IPs, and the newborn neurons. A multiscale formalism describing IP dynamics allows one to track the progression of cells along the subsequent phases of the cell cycle, as well as the temporal evolution of the different cell numbers. We have fitted the numerical outputs of the model to experimental cell numbers at different stages of embryonic development. We have compared wild-type mice with mice mutant for Ftm/Rpgrip1l (a gene involved in human ciliopathies with severe brain abnormalities). This study reveals a shortening of the neurogenic period associated with an increased influx of newborn IPs from apical progenitors at mid-neurogenesis in the mutant case. Additional information is provided on cell kinetics, such as the mitotic and S phase indexes, and neurogenic fraction.

Disclosure of Interest: None Declared

A multi-scale systems pharmacology approach for personalizing cancer chronotherapy

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Secondary topic : Multiscale Systems Biology

Your abstract : Cancer chronotherapeutics- that is administering anticancer drugs following the patient's biological rhythms over 24h- has nowadays proven its benefit regarding both toxicities and efficacy compared to constant administration. However, recent findings highlight the critical need for personalizing circadian delivery. Anticancer chemotherapy personalisation requires to reliably account for the temporal dynamics of molecular pathways of patient's response to drug administration. In a context where clinical molecular data is usually minimal in individual patients, multi-scale physiologically-based modelling stands as an adapted solution to describe protein networks ultimately responsible for circadian rhythms in treatment antitumor efficacy and side effects.

Thus, a combined in silico-in vitro-in vivo approach is being undertaken for personalizing the circadian administration of irinotecan, one of the cornerstones of chemotherapies against digestive cancers. Irinotecan molecular chronopharmacology was studied at the cellular level in an in vitro/in silico investigation. Large transcription rhythms of period T= 28 h 06 min (SD 1 h 41 min) moderated drug bioactivation, detoxification, transport, and target in synchronized Caco-2 colorectal cancer cell cultures. These molecular rhythms translated into statistically significant changes according to drug timing in irinotecan pharmacokinetics, pharmacodynamics, and drug-induced apoptosis. Clock silencing through siBMAL1 exposure ablated all the chronopharmacology mechanisms. Mathematical modeling highlighted circadian bioactivation and detoxification as the most critical determinants of irinotecan chronopharmacology.

Next, a mouse investigation allowed for the identification of three classes showing different circadian pattern in irinotecan chronoPK, and intestinal and blood chronotoxicity. Further, an additional study focused on the sex-specific circadian rhythms of P-glycoprotein, one of the efflux transporters of irinotecan. These in vitro and in vivo studies are being used for the design of a mathematical model of the irinotecan whole-body chronoPK-PD in mice. Finally, a human model is being developed through a scale-up of the mouse model integrating several clinical databases of patients under irinotecan-based chemotherapy.

Disclosure of Interest: None Declared

Systems Neurosciences
SUNDAY, OCTOBER 28 – 04:00 PM – 05:40 PM

Modelling hyperpolarisation-gated synaptic plasticity in motor learning

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Secondary topic : Multiscale Systems Biology

Your abstract : When we look at a fixed point and move our head in one direction, our eyes reflexly move in the opposite direction in order to keep the image stable. When this reflex is disturbed, it needs to be re-calibrated. This happens in cells of the medial vestibular nucleus (MVN), which get two types of input: 1. Excitatory input from the vestibular nerve which relays information about head movement. 2. Inhibitory input from Purkinje cells which encodes the error signal if the image before and after head movement does not coincide. The interplay of inhibitory and excitatory stimuli can result in "hyperpolarisation-gated synaptic plasticity", where the inhibitory input from Purkinje cells causes potentiation or depression of the vestibular nerve synapse. This allows MVN neurons to adjust their gain, so that eye movement and head movement are back in sync. This hyperpolarisation-gated synaptic plasticity is different from plasticity found in other parts of the brain, notably Hebbian plasticity in the hippocampus, which relies on NMDA-receptor dependent depolarisation of the postsynaptic neuron. So far, the cellular and molecular mechanisms underlying hyperpolarisation-gated synaptic plasticity are poorly understood.

Here, we present a multi-scale computational model of hyperpolarisation-gated synaptic plasticity in MVN neurons. The model combines a simulation of cellular electrophysiology (in NEURON) with a detailed kinetic model of postsynaptic Calcium-activated signalling pathways (in Copasi). The readout is phosphorylation of AMPA receptors, as a proxy for long-term synaptic plasticity. We show that the close temporal succession of inhibitory and excitatory stimuli converging on a distal dendritic compartment can indeed produce synaptic plasticity, both in the form of a strengthening (LTP) or a weakening (LTD) of the synapse. We also show that this is crucially dependent on Calcium influx through LVA channels and on the balance between Calcium-activated kinases and phosphatases. We also show that the direction and strength of the effect depends on the intensity and duration of the inhibitory stimulus, as well as the relative timing of the inhibitory and excitatory stimuli. These findings reveal cellular mechanisms by which the cerebellum may regulate signal processing in motor pathways during motor learning.

Disclosure of Interest: None Declared

Robustness of controllability in structural brain networks

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Your abstract :

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The recent advent of connectomics has provided us with a huge amount of brain network data as well as a new way of understanding complex brain functions in view of network science. Recently, applying network control theory to brain networks has become an emerging issue, and the significance of network controllability in brain has also been validated based on clinical data. Since the brain itself is already an autonomously controlled system which governs the core functions of life at all times, we can infer that the control architecture of brain networks should have a certain degree of robustness in maintaining normal brain functions. In this regard, analysis of robustness of the network controllability in brain might provide a novel insight into the inherent control architecture of the brain and lead us to a deeper understanding of the organizational principle of the brain. However, there was no such an attempt. To tackle this problem, we have extracted structural brain networks of 100 healthy adults from the Human Connectome Project database, and also prepared the structural brain networks of other species for comparison. We have simulated various perturbations of the networks and analysed the resulting change of network controllability metrics. We further compared these results with those obtained from other types of complex networks. As a result, we found that brain networks have stronger robustness in their network controllability with respect to targeted attack. We also found that these results originate from the inherent control architecture of brain networks, which is different from other complex networks. The findings in our study provide a more advanced understanding of the operating principle of brain functions and contribute to designing a more effective therapeutic intervention for cognitive enhancement and treatment of complex brain disorder.

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Disclosure of Interest: None Declared

Systems biology applied to post-traumatic stress disorder to stratify into subtypes

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Secondary topic : Systems Neurosciences

Your abstract : INTRODUCTION: Combat-related Post Traumatic Stress Disorder (PTSD) is currently defined by self-reported psychological symptoms. Yet, the co-morbidities associated with the illness, involve inflammation, metabolic syndrome, non-attributable pain, as well as uncontrolled anger, hostility, and other actions which disrupt personal and working relationships. Furthermore, there seem to be various 'types' of PTSD (separate from severity) and concomitantly the success rate for PTSD treatment is ~60% effective, again suggesting the presence of subtypes. Focused molecular studies revealed some pathway information, so we took the approach to apply global multi-omic analyses integrated with clinical and physiological data in an effort to gain a more cohesive view of the illness and specifically develop a reproducible panel of blood-based biomarkers with good sensitivity and specificity to obtain an objective signature of PTSD for diagnosis and to aid in stratifying into illness subtypes.

METHODS: Four male subgroups consisted of a "discovery set" 82 PTSD cases, 80 controls, two "filtering sets" (36/24, and 28/10) and a "validation set" of 28/26 cases/controls. 'Omics technologies applied to these blood samples included global DNA methylation, miRNA, metabolomics, neuroendocrinology, extended proteomics, immune responses, standard blood chemistries, selected cell surface markers, extensive psychological and physiological testing.

RESULTS: Predicted PTSD probabilities for PTSD cases were positively correlated with multiple co-morbid clinical symptoms, including early trauma exposure, sleep disturbances, depression symptoms, combat-related PTSD exposure, as well as overall psychological health based on Clinician administered PTSD Scale (CAPS), and other instruments. Many covariates (age, BMI, etc) did not affect the diagnostic panels success.

DISCUSSION: The discovery of biomarker panels that reliably discriminate individuals with combat-related PTSD from those without PTSD, with adequate degrees of sensitivity and specificity, demonstrates the utility of the multi-omics/ bioinformatics approach. As additional, larger and more diverse PTSD samples are studied, as additional analytes are included in omics panels, and as phenotypic diagnoses of PTSD are refined, the next series of biomarker panels for PTSD can include our more recent data and additional cohorts and should achieve even greater degrees of sensitivity and specificity and improve subtype characteristics.

Disclosure of Interest: None Declared

Gene networks, neuron types, and brain circuits underlying common psychiatric disorders

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Secondary topic : Multiscale Systems Biology

Your abstract : Identification of cellular networks, neuron types, and brain circuits underlying common psychiatric disorders is a major challenge of modern genetics and neuroscience. Despite the identification of many relevant loci, molecular mechanisms of many common neurodevelopmental diseases remain unclear. We have developed several computational approaches that make it possible to integrate diverse genetic data using a unified statistical framework. The application of these approaches to several psychiatric diseases (autism, schizophrenia) allowed us to implicate several molecular processes involved in synapse development, axon targeting, neuronal mobility, and chromatin modification. To further probe the etiology of autism we combined genetics, brain area- and neuron-specific expression, and detailed phenotypic information from ASD patients. We observe that multiple cell types and brain areas are affected in autism, but the impact of ASD mutations is strongest in cortical interneurons, pyramidal neurons and the medium spiny neurons of the striatum, implicating cortical and cortico-striatal brain circuits. In females, truncating ASD mutations on average affect genes with 50-100% higher brain expression than in males. We will also present analysis of phenotypic consequences of specific mutations in human genes with distinct functional roles and temporal expression profiles.

Disclosure of Interest: None Declared

Developmental Systems Biology B
MONDAY, OCTOBER 29 – 04:00 PM – 05:40 PM

Simulating cellular movements in early C. elegans embryogenesis

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Secondary topic: Methodological developments for Systems Biology

Your abstract: Understanding how cells position themselves correctly in multicellular environments is a fundamental challenge in developmental biology. We use the invariable embryogenesis of C. elegans and a modelling approach to better understand the underlying mechanisms driving cellular movements. We developed a simulator to model the physical interactions among cells that influence cell motion, including physical constraints, cell division, adhesion, and active forces. To inform and evaluate simulations we use a dataset of real embryos with microscopy tracked nuclei positions. In the model cells are represented as soft spheres that can repulse and adhere to each other, and also move and divide. Cell division timings and movement directions are taken from the dataset. The egg shell repulses the cells and is modelled as a convex hull whose shape is derived from the embryo dataset. We use the model to unravel the contribution of purely physical processes in early embryogenesis, such as the spatial constraints, egg shape, and shape changes due to divisions, and active biological phenomena such as differential adhesion and active movements. The problem is framed as a machine learning approach to find the correct cellular positioning, where hypotheses are evaluated by learning optimal parameter values on a training set and testing how much they improved cellular positioning. To optimize the model parameters we used evolutionary algorithms. Differential evolution is used for continuous variables and a novel molecule-based evolution scheme optimizes the differential cellular adhesion. At the 8-cell stage our simulations highlight previously described phenomena, such as a weak basal adhesion force among all cells and active movements for the ABpl and ABpr cells. Also adhesion between E and P3 is suggested, which matches published results of how descendants of both cells adhere during gastrulation. Our main goal however is to reproduce the complex movements during the AB64 stage. We are currently evaluating our predictions for this phase with experimens, by visualizing e-cadherin molecules, cell shapes and the actomyosin network. As a perspective, we are expanding our simulator with a signaling model. Cell signaling is represented as a network of reactions expressed as logic rules, where signals trigger cascades and determine cell fate. By modelling how signals affect fate, linking fate to cell behavior, we can predict the effects of perturbations on cell fates and positions.

Disclosure of Interest: None Declared

Making and erasing patterns in the tooth field: lessons from Edar dynamics and mathematical modeling

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Your abstract: Patterning, the process whereby patterns arise during development, is generally viewed as a directional, straightforward process. However, biological systems are the product of evolution that proceeds as a “tinkerer” more than as an “engineer”. Do developmental systems also take circuitous routes? Here, we studied mouse molars, whose evolutionary history is well known. Premolars were lost during evolution and previous studies have shown that the sequential patterning of molar signaling centers is initiated by abortive signaling centers thought to be premolar vestiges. We report the exquisite temporal dynamics of Edar gene expression pattern, that reveals successive phases of pattern making and pattern erasing in the tooth field, a phenomenon we called a developmental palimpsest. Mathematical modeling of this dynamics lead to a 2-steps model of activation-inhibition mechanisms in the growing tooth field: 1- the tissue is primed by a traveling wave driving unfocalized activation, 2-priming raises inhibition and switches the system to a Turing regime, resulting in a focalized pattern. The model, thought to recapitulate the erasing of the R2 vestigial signaling center, correctly predicted its surprising rescue in the context of increased inhibition of the *Edar* mutant. It also predicted that R2 signaling center is actively competed by the wave of activation preceding the formation of the first molar signaling center, what we confirmed experimentally by physically separating the two signaling centers in tooth cultures. Finally, Edar expression revealed that R2 recovers from the palimpsest and transiently co-exists with M1 signaling center. In the lower jaw, but not the upper jaw the two signaling centers then fuse into a single large signaling center. We show that this behavior is Edar-dependent, and recapitulated by introducing chemotaxis as a secondary process of tooth germ maturation. In conclusion, we have uncovered the highly indirect nature of pattern formation in the molar field. Studying the dynamics of the system with simple mathematical models lead to a better understanding of this system. Our study argues for a better appreciation of temporal dynamics in pattern formation.

Disclosure of Interest: None Declared

3D mechanical stress patterning during flower morphogenesis

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Secondary topic : Developmental Systems Biology

Your abstract : Plant morphogenesis relies heavily on mechanics. Not only because deformations of living matter — like any kind of matter — necessary require stresses but also because meristematic cells are stress-sensitive: They can tune their behavior in response to mechanical cues. Estimation, visualization & quantification of stress patterns undergone by plant tissues is therefore of prime importance to understand the individual responses of their constitutive cells.

Though this profound intertwining between mechanics & developmental biology has been investigated intensively over the past decade, we still lack precise & quantitative knowledge of these stress patterns.

To address this issue, we developed a computational pipeline to simulate the mechanical response of plant tissues to turgor-induced loading. Applied to high fidelity finite elements meshes generated from 3D confocal images of real growing tissues, this pipeline enabled us to simulate the mechanical behavior of several hundreds of cells organized in multiple layers with sub-cellular resolution. In conjunction, we investigated the influence of tissues geometrical & topological characteristics on stress fields experienced by cells through the use of artificially-generated cellularized templates.

Our analysis leads to the following conclusions:

i) Inner tissues influence stress field within the epidermis in a curvature-dependent manner. This challenges the idea that saddle-shaped regions, such as frontiers between meristems & lateral organs, experience high intensity tangential stresses.

ii) Our simulations revealed a strong correlation between tangential stress intensity & cells surface area. This echoes similar results recently obtained by others in the case of pavement cells & suggests that such a correlation between cell size & stress intensity could be a key feature of mechanosensitive signaling in plant tissues.

iii) Epidermal & inner cells appear to experience radically different stress patterns.

Put together our results raise the question of the relevance of mechanical forces as positional cues during development: The influences of various multi-scale geometrical features (*e.g.* cell shape, organ curvature) are intertwined in turgor-induced stress fields. Mechanosensitivity limited to specific components of these fields could be an efficient way for cells to select & respond to specific geometrical characteristics during morphogenesis.

Disclosure of Interest: None Declared

Enhancer function underpins essential properties of gene regulatory networks for patterning precision

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Secondary topic : Modelling Networks and Circuits

Your abstract : Developmental patterning results in an initially homogeneous tissue of cells choosing different fates in a spatially organised manner. The position and precision of gene expression patterns is therefore crucial for development. We use the vertebrate ventral neural tube as a well-characterised example of patterning. In this tissue, a gradient of Sonic Hedgehog is interpreted by a gene regulatory network (GRN) that divides neural progenitors into molecularly distinct domains arrayed along the dorsal-ventral axis. Mathematical models have been developed that describe the GRN and capture the position of the domains in the wild type (WT) as well as in multiple mutants. We derive a stochastic model that captures the *in vivo* position and precision of gene expression in wild-type and mutant embryos. Analysis of this model suggested a mechanism that accounts for patterning precision in which the fluctuation of protein levels at the boundary between domains is structured in a way to ensure boundary sharpness. We tested this model *in vivo* by mutating enhancers predicted to contribute to the precision and position of boundaries. Quantification of the *in vivo* behaviour was consistent with the proposed mechanism. Together the analysis highlights how a tissue level property – the precision of domains of gene expression – arises from the dynamics of a gene regulatory network.

Disclosure of Interest: None Declared

Wet-tip versus dry-tip regimes of osmotically driven bile flow in the liver

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Your abstract: The secretion of osmolites into a lumen and thereby caused osmotic water inflow drive fluid flows in organs without a mechanical pump, as opposed to the heart in blood circulation. Such fluids include saliva, sweat, pancreatic juice and bile. The effects of elevated fluid pressure and the associated mechanical limitations of organ function remain largely unknown since fluid pressure is hardly measurable inside tiny secretory channels.
We consider the pressure profile of the coupled osmolite-flow problem with combined velocity and pressure boundary conditions that reflect the asymmetric geometry of a secretory channel with one closed and one open end. Notably, the entire lateral boundary acts as a fluid source, the strength of which is determined by feedback from the emergent pressure solution itself. Hence, the pressure gradient between the boundaries is not imposed but self-organises.
We derive analytical solutions for the one-dimensional spatial dependencies along the channel and compare them to numerical simulations of the problem in three-dimensional space. The theoretical results reveal fundamental parameter dependencies and a phase boundary in a four-dimensional parameter space separating the commonly considered ``wet-tip'' regime with steady flow out of the very tip of a channel from a ``dry-tip'' regime suffering stalled flow.
We validate model predictions against intra-vital video microscopy data from mouse [1] and propose a relation between the predicted phase boundary and the onset of cholestasis, a pathological liver condition with reduced bile outflow.
[1] Meyer et al. (2017) A predictive 3D multi-scale model of biliary fluid dynamics in the liver lobule. Cell Systems 4, 277–290.e9. DOI:10.1016/j.cels.2017.02.008

Disclosure of Interest: None Declared

Evolutionary and Ecological Systems Biology
MONDAY, OCTOBER 29 – 04:00 PM – 05:40 PM

Quantifying spatiotemporal dynamics and noise in microbiome studies using replicate sampling

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Secondary topic : Multiscale Systems Biology

Your abstract : Metagenomic sequencing has enabled detailed investigation of hundreds of diverse microbial communities, but in-depth profiling of their spatiotemporal dynamics remains challenging. We have developed a widely applicable method based on replicate sampling and spike-in sequencing, and a mathematical model to separately quantify the contributions of temporal variation, spatial sampling heterogeneity and technical noise to absolute bacterial abundance measurements. To demonstrate the utility of our approach, we combine 16S and metagenomic shotgun sequencing with a custom spike-in approach to conduct the first high-resolution time series study of absolute human gut microbiota abundances. Our method reveals the complexity of spatiotemporal dynamics in the human gut microbiome and unmasks key ecological features hidden from previous analyses.

Disclosure of Interest: None Declared

High-order interactions and the predictability of function in microbial consortia

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Secondary topic : Multiscale Systems Biology

Your abstract : Microbial communities carry out critical biochemical functions throughout the biosphere: from nitrogen fixation and photosynthesis to the recycling of nutrients and the decomposition of inert organic matter. These functions depend very strongly on community composition: i.e., on which species are present and in what numbers. Can we manipulate community composition to accomplish desirable functional outcomes? If predicting function in such a bottom-up manner were generally feasible, this would encourage synthetic approaches to designing complex communities in a rational manner, by mixing and matching components with known functional traits. Here, we have addressed this problem by focusing on a simple community-level function that can be quantitatively modelled on solid biochemical grounds: the amylolytic activity of combinatorial assemblages of seven starch-degrading soil bacteria. This allows us to formulate a null model that is based on the theory of enzymatic kinetics and validate it experimentally. Armed with that, we are able to unambiguously show that high-order interactions often dominate the functional landscape of our microbial consortia. More broadly, our study suggests that high-order functional interactions may be generically prevalent in microbial communities, presenting a fundamental challenge to predict their function from the bottom-up.

Disclosure of Interest: None Declared

The percolation of metabolism and bacterial lifestyle and evolvability

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Secondary topic : Multiscale Systems Biology

Your abstract : How the structures of biological networks constrain their function and evolutionary plasticity, and how they reflect the lifestyle and phenotypic properties of species, are central questions of systems biology. Graph-based comparisons of biological networks have previously shown structural differences between groups of organisms; however, how these differences correspond to specific molecular and evolutionary mechanisms remains poorly understood. In this work, we used more than a thousand genome-scale bacterial metabolic reconstructions to investigate the interaction between metabolic network structure, function, and bacterial lifestyle and evolvability. Specifically, we describe the occurrence of a percolation transition as a function of bacterial metabolic network size. We found that networks below a certain number of reactions—corresponding to a critical genome size—display a sharp decrease in the fraction of metabolites that they can interconvert at steady state. Below this critical size, the nutritional fastidiousness of microbes increases, and metabolic networks become less likely to acquire new phenotypes through the horizontal gain of additional reactions. The transition also coincides with marked differences in the fraction of obligate symbiotic and parasitic lifestyles, the complexity of known growth media, and the probability of metabolic cross-feeding among pairs of bacteria. Additionally, the fraction of genes devoted to transcriptional regulation, signaling, and metabolism drop more rapidly with decreasing genome sizes below the transition. Altogether, our results suggest that adaptation to stable and rich nutrient environments facilitates a physical transition in metabolic network architecture distinguishing bacteria with different lifestyles, regulatory complexity, and phenotypic and evolutionary plasticity.

Disclosure of Interest: None Declared

Systematic evaluation of conditional gene essentiality changes across genetic backgrounds in Saccharomyces cerevisiae

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Secondary topic : Multiscale Systems Biology

Your abstract : Most of modern genetics is based on comparisons against a reference individual, for which the most molecular data has been collected. For instance, in genotype-to-phenotype models the information on gene's conditional essentiality is used to prioritize variants likely to cause a loss of function phenotype. However, it has been observed that gene essentiality can vary upon its interaction with a specific genetic background (epistasis), undermining the application of this approach. Understanding the magnitude of this phenomenon and its mechanism is of paramount importance for the development of precision genetic interventions. Here we present a chemical genomics experiment carried out using 4 *Saccharomyces cerevisiae* strains tested across ~40 conditions. Despite a general correlation of chemical genomics profiles between orthologs, we observed a change in conditional essentiality for a large number of genes across the 4 strains. Interestingly, the genes observed to change their essentiality profile more often have a greater propensity in participating in genetic interactions. When focusing on protein complexes and functional units we observed an overall higher conservation of chemical genomics profiles across strains, potentially pointing out to a "buffering" effect. We also carried out a joint genome-wide association analysis between common and rare variants using a recently published panel of ~1000 *S. cerevisiae* natural isolates. Taken together, we believe this data will yield useful insights on the mechanisms behind conservation of gene function.

Disclosure of Interest: None Declared

Natural transformation: acquisition and removal of mobile genetic elements in stochastic environments

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Your abstract: Horizontal gene transfer (HGT) drives the propagation of genes in bacterial communities. This is of prime importance for human health when these genes provide antibiotic resistance. HGT may result from the activity of mobile genetic elements (MGE), using conjugation and transduction mechanisms, or from mechanisms encoded by bacteria themselves such as natural transformation. The role of natural transformation in the adaptability of bacteria by acquiring new genes is well acknowledged. However, a new paradigm proposes that the main role of transformation is rather to cure genomes from parasitic or obsolete genetic elements by replacing them by non-deleterious DNA. This hypothesis would explain why several MGEs, as an evolutionary response, inhibit the transformation of their host cell by disrupting the competence machinery or by carrying genes coding for DNases. Here, we propose to conciliate these antagonistic aspects of natural transformation. Although MGEs may be useful for cells in some conditions, they are usually costly when these conditions are not met. This is the case of antibiotic resistance genes, which prevent cell death upon antibiotic exposure but are an unnecessary burden otherwise. Thus, in stochastic environments, bacteria could benefit from the double role of natural transformation to acquire and remove MGEs to maximize their overall fitness. Using a computational model, we show that, under stochastic antibiotic treatments, natural transformation allows the acquisition of antibiotic resistance genes carried by MGEs but also the restoration of the former susceptible genotype. This restoration is allowed by genetic configurations providing enough insertion sites for MGEs which enable to reform the former genotype by recombination. The model also shows that, under stochastic exposure to different antibiotics, the acquisition of resistance genes and the cure of the genomes is facilitated by MGEs aggregating resistance genes, making them predominant. Thus, the double function of transformation could explain the relative stability of bacterial genomes and the accumulation of resistance genes on MGEs.

Disclosure of Interest: None Declared

Methodological developments for Systems Biology A
MONDAY, OCTOBER 29 – 10:50 AM – 12:30 PM

Enzyme and substrate concentrations in cellular reaction networks at maximal growth rate

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Secondary topic : Quantitative Systems Physiology

Your abstract : The most widely-used methods for genome-scale cellular modelling, such as Flux Balance Analysis (FBA), are capable of powerful predictions in certain settings (1), but fail at quantitative predictions for growth rates and protein expression. One possible reason for their limited predictive power may be their failure to account for metabolite concentrations and the resulting non-linear reaction kinetics. The computational complexity associated with such non-linear constraints currently seems an obstacle too great for genome-scale simulations (2); a key for building more powerful models of cell growth would be the reduction of the solution space through quantitative organizing principles that guide the cellular resource investment into different molecule types. Previously, we have shown (3) that the minimization of the total cost of enzymes and their substrates results in a simple and accurate relationship that depends only on the respective enzyme affinity in the case of irreversible reactions. Here, we present an analytical solution for the genome-scale balance of cellular concentrations in the more general problem of maximizing cell growth rate under major biochemical and biophysical constraints: the dilution of all cell components by growth, mass conservation, reaction kinetics, the necessary investment into protein production, and the limited solvent capacity of the cytosol. Our theoretical result provides a novel, universal framework for the study of cell growth and metabolism, explicitly connecting Elementary Flux Modes, Flux Balance Analysis, and Metabolic Control Analysis into one unified framework. Our mathematical formulation further indicates a path towards efficient methods of whole-cell simulation that explicitly account not only for the major biochemical and biophysical cellular constraints, but also for the concentrations of all important cellular components.

(1) Orth, JD et al. (2010) Nat Biotechnol 28, 245.
(2) Schuster, S et al. (2011) BioSyst 105, 147.
(3) Dourado et al. (2017), bioRxiv 128009.

Disclosure of Interest: None Declared

Using dynamical reaction network to infer drugs selectivity in pharmacology

Romain Yvinec[* 1], Marion Deffarges[1], Mohammed Akli Ayoub[2], Francesco De Pascali[1], Laura Riccetti[3], Jorge Gandia-Sanchez[1], Lucie Pellissier[1], Pascale Crépieux[1], Eric Reiter[1], Anne Poupon[1]
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Secondary topic : Modelling Networks and Circuits
Your abstract : An active area of research in pharmacology and drug discovery applies to functional selectivity (or biased agonism, biased signaling): the ability of a ligand to selectively activate some signal transduction pathways as compared to the native ligand acting at the same receptor. Applications of functional selectivity are numerous for therapeutics, as it allows triggering a more specific response, thus limiting undesired effects.

At the theoretical level, biased signaling is supported by the concept of conformational selectivity: a given receptor may adopt several conformations, that can be stabilized by its interaction with a ligand, and each of these conformations potentially activates the downstream signaling pathways with different efficacies.

At the practical level, experimentalists seek to quantify ligand bias in order to classify ligands according to their selectivity. One popular method uses the so-called operational model (Black and Leff, Proc. R. Soc. Lond. B, 1983) to fit dose-response curves (having a sigmoidal shape). From such fit, and using the pharmacological notion of affinity and efficacy, one may infer a transduction coefficient for each ligand/response couple. A bias coefficient is then calculated by comparing transduction coefficients and standard statistical tests assess its significativity.

We have performed such a method with our in-house generated data on the FSH and LH/CG receptors[a,b], and revealed parameter identifiability issues. More importantly, the use of “static” data given by dose-response appeared problematic, as ligand responses may have various dynamic patterns linked to different cellular outcomes.

Using dynamic BRET measurements, we will motivate the use of dynamic ODE reaction network modeling of signaling responses to decipher ligand bias. In particular, after finding a model that appropriately fit our dynamic responses for each ligand, we use L1 penalization (Steiert et al., Bioinformatics 32(17) 2016) to infer ligand-specific kinetic rate parameters. We thus propose a new definition of ligand bias as the minimal set of kinetic parameters that differs from a reference ligand.

[a] Ayoub et al., *Profiling of FSHR Negative Allosteric Modulators on LH/CGR Reveals Biased Antagonism with Implications in Steroidogenesis,* Molecular and Cellular Endocrinology 436 (2016)
[b] Riccetti et al., *Human Luteinizing Hormone and Chorionic Gonadotropin Display Biased Agonism at the LH and LH/CG Receptors*, Scientific Reports, 7: 940 (2017)

Disclosure of Interest: None Declared

Detecting epistasis using random forest

Corinna Schmalohr[* 1], Jan Grossbach[1], Mathieu Clément-Ziza[2], Andreas Beyer[1, 2]
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Secondary topic : Multi-omics

Your abstract : When studying the influence of genetic factors on phenotype variation, non-additive genetic interactions (i.e., epistasis) have to be taken into account. However, there is a lack of methods that can reliably detect such interactions, especially for quantitative traits. Random Forest (RF) has been shown to outperform other methods at detecting genetic associations, which was mainly attributed to its ability to take epistasis into account. However, RF does not give any information about which specific genetic variants interact. Therefore, we propose three new approaches that exploit the structure of RF decision trees for the detection of epistasis. We termed these methods 'paired selection frequency', 'split asymmetry', and 'selection asymmetry'. Since they complement each other for different epistasis types, an ensemble method that combines the three approaches was also created. We applied our approaches to multiple simulated scenarios and two different real datasets from different *Saccharomyces cerevisiae* crosses. They were compared to the commonly used exhaustive pair-wise linear model approach, as well as several two-stage approaches, where loci are pre-selected prior to interaction testing. The Random Forest-based methods presented here generally outperformed the other methods at identifying meaningful genetic interactions both in simulated and real data.

Applying these methods to large quantitative genetics datasets could help elucidate how epistatic effects contribute to phenotypic variance. Thus, the approaches presented here extend the applicability of Random Forest for the genetic mapping of biological traits. Since RF has many applications outside of genetic association, this work represents a valuable contribution not only to genotype-phenotype mapping research, but also to other scientific applications where interactions between predictors in a RF might be of interest.

Disclosure of Interest: None Declared

SMILES-based prediction of drug-target interaction binding affinity

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Secondary topic : Systems Medicine

Your abstract : Identification and prediction of drug-target interaction (DTI) information is a major research question in drug discovery. As of last decade, the research in this area has been accelerated with the integration of new methodologies that are introduced with the developing technologies enabling high computation capacity. However, most of the studies published in DTI domain treat DTI prediction as a binary classification problem, whereas in reality, drug-target pairs have binding affinity values indicating the strength of the interaction.

In this study, we propose a novel methodology to predict drug-target interaction binding affinity using only ligand SMILES information. We represent proteins using the word-embeddings of the SMILES representations of their ligands. We recently showed that this ligand-based protein representation performs as well as protein-sequence based representation methods in protein clustering problem. We propose to enhance DTI information by using this novel representation method and providing a prediction model to find new candidate interactions using deep learning approaches to build a state-of-art model that is strictly text-based.

Disclosure of Interest: None Declared

Modelling Networks and Circuits A
MONDAY, OCTOBER 29 – 10:50 AM – 12:30 PM

E. coli can survive stress by noisy growth modulation

Om Patange[* 1, 2], Christian Schwall[1, 2], Matt Jones[1], Douglas Griffith[1], Andrew Phillips[3], James Locke[1, 2]
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Secondary topic : Quantitative Systems Physiology

Your abstract : Gene expression can be noisy, as can the growth of single cells. Such cell-to-cell variation has been implicated in survival strategies for bacterial populations. However, it remains unclear how single cells couple gene expression with growth to implement these survival strategies. Here we show how noisy expression of a key stress response regulator, *rpoS,* allows *E. coli* to modulate its growth dynamics to survive future adverse environments. First, we demonstrate that *rpoS* has a long-tailed distribution of expression in an unstressed population of cells. We next reveal how a dynamic positive feedback loop between *rpoS* and growth rate produces multi-generation *rpoS* pulses, which are responsible for the *rpoS* heterogeneity. We do so experimentally with single-cell, time-lapse microscopy and microfluidics and theoretically with a stochastic model. Finally, we demonstrate the function of the coupling of heterogeneous *rpoS* activity and growth. It enables *E. coli* to survive oxidative attack by causing prolonged periods of slow growth. This dynamic phenotype is captured by the *rpoS*-growth feedback model. Our synthesis of noisy gene expression, growth, and survival paves the way for further exploration of functional phenotypic variability.

Disclosure of Interest: None Declared

The triangle of ageing: a model of the accumulation of damaged proteins in Saccharomyces cerevisiae shows how retention enables replicative ageing

Johannes Borgqvist[*1], Niek Welkenhuysen[1], Marija Cvijovic[1]
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Your abstract: Accumulation of damaged proteins is a hallmark of ageing occurring in organisms ranging from simple bacteria and yeast to mammalian cells. During cell division in yeast, damaged proteins are retained within the mother cell resulting in a new daughter cell with full replicative potential and an ageing mother cell with a finite replicative lifespan (RLS). However the cell-specific features determining the lifespan remain elusive. It has been suggested that the RLS is dependent on the ability of the cell to repair and retain pre-existing damage. To deepen the understanding of how these factors influence the life span of individual cells we have developed the first dynamic model of damage accumulation in budding yeast accounting for replicative ageing. The model includes five essential properties namely cell growth, formation of damage, repair of damage, cell division and cell death. Based on these, we derive the **triangle of ageing**: a complete theoretical framework describing the conditions allowing for replicative ageing, starvation, immortality or clonal senescence. Exploiting this framework we propose that the retention mechanism is a fundamental force underlying ageing and in fact it allows for a high RLS and healthy progeny. Furthermore, we suggest that resilience to damage is a central trait governing the replicative ageing and can be used as a basis for life prolonging strategies. In addition, the model is in agreement with experimental data consisting of RLS distributions and mean generation times from populations of three strains of *Saccharomyces cerevisiae*: the short lived ΔSir2, the wild type Wt and the long lived ΔFob1 which validates the underlying assumptions and we conclude that strains with an efficient repair machinery require retention. Finally, the triangle of ageing suggests that replicative ageing is tightly linked to asymmetrical cell division and that symmetrically dividing organisms such as *Schizosaccharomyces pombe* or *Escherichia coli* do not exhibit age-related phenotypes on account of prioritising cell growth over retention of damage. Thus, the proposed model indicates that in order to obtain a mechanistic understanding of the ageing process in eukaryotic organisms it is critical to investigate the constituents of the retention machinery.

Disclosure of Interest: None Declared

Emergence of non-genetic heterogeneity in metabolic reactions

Mona Tonn[*1], Philipp Thomas[1], Mauricio Barahona[1], Diego Oyarzún[1]
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Your abstract: Heterogeneity is a hallmark of cell physiology and appears in most layers of the cellular machinery. Metabolic heterogeneity, in particular, underpins various single-cell phenomena such as drug tolerance and growth variability in microbes. Much research has focussed on the heterogeneity of the proteome, yet it remains unclear whether such variation permeates to metabolism and shifts the metabolic state of a cell.

We introduce a stochastic model which integrates a mechanism for stochastic gene expression with Michaelis-Menten kinetics. The model shows that complex forms of heterogeneity emerge from the interplay between fluctuations in enzyme expression and catalysis. The analysis predicts clonal populations to split into two or more metabolically distinct subpopulations. We reveal previously unknown mechanisms for metabolic bimodality and patterns of multimodality originating from the kinetic reaction which are not seen in deterministic models. We show that metabolic behaviour can be accurately approximated by a Poisson Mixture Model which is valid for a wide range of parameters.

Our results cast light on the link between cellular stochasticity and variability of metabolic phenotypes, providing a widely applicable theory to probe the sources of metabolic heterogeneity and predict metabolic heterogeneity from single-cell proteomics data.

Disclosure of Interest: None Declared

Functional topology of the E. coli small molecule regulatory network

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Secondary topic : Multiscale Systems Biology

Your abstract : Small-molecule regulation is a fundamental element of metabolic flux stability and control, yet remains largely unexplored and unexplained at a systemic level. This is despite the fact that many metabolic transitions are governed at least in part by regulation at the metabolic level. Recent work has laid the foundation for the systematic construction and analysis of small-molecule regulatory networks (SMRNs); in this vein, we present a genome-scale SMRN reconstruction for *E coli* and characterize its features from global to local scale to both broadly explain the phenomenon and to make specific predictions about functional interactions between metabolic modules and pathways. Our expanded core network consists of 973 reactions and approximately 4000 regulatory interactions collated from BRENDA and the Allosteric Database. Global structure analysis of this network reveals scale-richness among regulatory nodes, and suggests that the organization of regulatory interactions maximizes information entropy in the network. Thus we find that topologically local regulatory structures, or motifs, define SMRN organization. Within the SMRN motifs, we find the eight canonical feedforward loops at varying frequencies alongside several novel feedforward structures that combine catalytic and regulatory interactions between reactions. In contrast to the transcriptional regulatory network, incoherency among regulatory motifs dominates in the SMRN. Kinetic modeling of both motif types demonstrates that the former are involved in coordinating otherwise unlinked fluxes in disparate metabolic modules, while the latter function to balance flux into juncture points in the metabolic network. These results suggest that small-molecule regulation functions in opposition to transcriptional regulation, and demonstrates the exact mechanisms by which the SMRN stabilizes the metabolic network. Additionally, we suggest that our analysis could be used to inform better predictions of metabolic flux distributions in response to changing environments and/or to identify key targets to disrupt the SMRN.

Disclosure of Interest: None Declared

Transcriptional regulation out of equilibrium: theory and experiment

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Your abstract : Transcription is a dynamic non-equilibrium process. Here, we provide a parsimonious framework for analyzing transcriptional regulation based on temporal modulations of key gene states – transcriptionally inactive, active and refractory. Our theory shows that how sensitively a gene responds to a regulator (activator or repressor) is controlled by the effect of the regulator on the speed of the transcription cycle: A transcription factor (TF) that shortens gene-state lifetimes causes more sensitive transcriptional responses than the standard equilibrium model of gene regulation would predict; conversely, a TF prolonging gene state lifetimes causes less sensitive responses. As a consequence, transcriptional activators that modulate the frequency of transcription bursts can trigger transcription at maximal rate through weak occupancy of their binding sites. We verify this prediction experimentally, using light-controlled gene activation by the GATA-type TF White Collar Complex (WCC) in *Neurospora*. Moreover, we find that burst frequency modulation by WCC allows for differential activation of its target genes independent of TF affinity. Data-based modeling indicates that differential gene regulation is due to the different gene activation rates after WCC binding, and we support this prediction using synthetic gene constructs. Finally, we show that refractory genes can be switched on more rapidly than non-refractory genes. In sum, our work demonstrates the relevance of a kinetic, non-equilibrium framework for understanding transcriptional regulation.

Disclosure of Interest: None Declared

Multi-omics
MONDAY, OCTOBER 29 – 04:00 PM – 05:40 PM

Causal and mechanistic pan-cancer immune regulatory network deciphered using systems genetics network analysis (SYGNAL)

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Secondary topic : Systems Medicine

Your abstract : The SYstems Genetics Network AnaLysis (SYGNAL) pipeline and transcription factor (TF)-target gene database was developed to decipher transcriptional regulatory networks from multi-omic and clinical patient data. We applied the SYGNAL pipeline to the more than 10,000 tumors across 33 diverse cancer types. The SYGNAL pipeline discovers directed flows of information anchored by somatically mutated genes or pathways to the TFs or miRNAs whose expression they modulate to the downstream co-regulated target gene clusters. Functional enrichment studies and association with patient survival are used to discover disease relevant clusters. Association with lymphocyte fraction (inferred from methylation profiles) and enrichment with immunomodulators allowed the discovery of 171 immune-associated clusters. There were 56 mutations modulating the activity of 21 TFs upstream of the 171 immune-associated biclusters which contained 27 immunomodulators. Every one of the 21 TF regulators has been implicated in the regulation of immune response (ETSs, IRFs, KLF2, NFATC1, NFKBs, PRDM1 and its paralog ZNF683, SPI1, and STATs). Interestingly, the regulators driving each immunomodulator could be shared between tumors, but the upstream somatic mutations modulating the regulators were not shared. For instance, STAT4 which regulated BTN3A1 and BTN3A2 in both LUSC and UCEC has TP53 and ARHGAP35, respectively, as the causal mutations driving STAT4 expression. Even when the same gene is significantly somatically mutated in at least two cancers the downstream regulator was different. For example, both LUSC and UCEC have TP53 as a somatic driver mutation, but in LUSC TP53 modulates STAT4 whereas in UCEC TP53 modulates IRF7. The unique complement of genes expressed in a given cell type modifies the response to a specific somatic mutation. Thus we propose that each tumor type would require a different set of mutations to modulate the activity of factors regulating genes that drive cancer phenotypes (e.g. the hallmarks of cancer).

Disclosure of Interest: None Declared

Dynamic metabolomics and phosphoproteomics reveal that insulin primes the adipocyte for glucose metabolism

Katsuyuki Yugi[* 1, 2], James Krycer[3], Shinya Kuroda[4], David James[3]
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Secondary topic : Modelling Networks and Circuits

Your abstract : Trans-omics is a discipline that aims to reconstruct a global and multi-layered molecular network, not as a group of indirect statistical correlations but as chains of direct mechanistic interactions (Yugi *et al.*, ***Cell Rep*** 2014; Yugi *et al.*, ***Trends Biotechnol*** 2016; Yugi and Kuroda, ***Cell Syst*** 2017; Yugi and Kuroda, ***Curr Opin Syst Biol*** 2018). The network reconstruction is performed based on comprehensive measurement data of multiple omic layers not taken from heterogeneous sources but measured under an identical condition. We applied methodologies of trans-omics to reveal how insulin acts on adipocyte metabolism in a global manner by integrating phosphoprotome and ^{13}C-labeled metabolome data (Krycer *et al.*, ***Cell Rep*** 2017). It has been thought that the major role of insulin is to provide anabolic substrates by activating GLUT4 transporter-dependent glucose uptake. However, a recent phosphoproteomic analysis showed us that insulin provides widespread phosphorylation changes in the metabolic enzymes of the adipocyte (Humphrey *et al.*, ***Cell Metab*** 2013), and it is unclear how these changes influence the dynamics of glucose metabolism upon insulin exposure. To examine the implications of phosphorylation of these metabolic enzymes, we performed dynamic tracer metabolomics in cultured adipocytes treated with insulin. By combining phosphoproteome and ^{13}C-labeled metabolome data, we found that insulin-dependent phosphorylation of metabolic enzymes occurs significantly early before glucose transport begins. This allows activation of key anabolic pathways that guide glucose influx into particular pathways where substrate metabolites are needed. We propose that this is a demand-driven system complementing a supply-driven mechanism by substrate accumulation. We named this phenomenon 'metabolic priming', a phenomenon in which insulin signaling kick starts catabolic reactions that generate a thermodynamic driving force that eventually pulls glucose into specific anabolic pathways.

References

Krycer *et al*., ***Cell Rep.*** 21, 3536–3547 (2017)
Humphrey *et al*., ***Cell Metab.*** 17, 1009-1020 (2013)
Yugi *et al*., ***Cell Rep*.** 8, 1171-1183 (2014)
Yugi *et al*., ***Trends Biotechnol.*** 34, 276–290 (2016) Cover Article
Yugi and Kuroda, ***Cell Syst.*** 4, 19-20 (2017)
Yugi and Kuroda, ***Curr. Opin. Syst. Biol.*** 8, 59-66 (2018)

Disclosure of Interest: None Declared

Emergence of the spatio-temporal replication program: role of origin distribution heterogeneity and 3D chromatin structure

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Secondary topic : Modelling Networks and Circuits

Your abstract : We recently proposed a model of the spatio-temporal DNA replication program with natural hypothesis that reproduces the DNA replication kinetics (Arbona 2018). In this model, fork-component recycling and potential replication origins (p-oris) localization explain that the frequency of origin firing per length of unreplicated DNA, *I(t),* presents a universal bell shape in eukaryotes (Goldar, 2009). Our model predicts that the maximum value for *I(t)* is proportional to the square of the density of p-oris and to the replication speed. Without free parameter, this relationship holds for 5 species with up to a 300 fold difference of I_{max}. We will first discuss how this model also captures the observation of a 16 fold increase of yeast S-phase in presence of hydroxyurea (HU) (Alvino 2007), consistently with the molecular action of the replication checkpoint induced by HU.
In higher eukaryotes, the positioning, number and strength of potential origins are still under debate. This model with few free parameters is a solid basis to study how spatial observables such as Mean Replication Timing (MRT) profiles can emerge from inhomogeneous distribution of potential origins. These distributions are drawn from experimental origin positioning signals (ORC binding sites, short nascent strand and replication bubble localization) or from chromatin mark profiles that have been associated to replication initiation (e.g. DNase I sensitivity, Gindin 2014). Comparison of model simulations with low resolution (~100 kb, MRT) and recent high resolution (~5 kb, replication fork directionality, Petryk 2015) experimental profiling of the replication program provides original information about the mechanisms underlying replication origins specification in higher eukaryotes. Finally, we will discuss 3D molecular dynamics simulations of our model where chromosomes are confined in a spherical nucleus, and firing factors are free to diffuse and to bind to proximal p-oris to initiate replication. When simulated chromosome structure presents both open (euchromatin) and more compacted (heterochromatin) structural domains compatible with chromosome conformation (HiC) data, firing-factor DNA accessibility profiles reproduce quite well DNase I sensitivity profiles and naturally explain the experimentally observed early and late MRT domains in human.

Arbona 2018, eLife 7:3519
Goldar 2009, PLoS One 4:5899.
Alvino 2007, Mol. Cell Biol 27:6396
Gindin 2014, Mol Syst Biol 10:3
Petryk 2016, Nat Commun 7:10208

Disclosure of Interest: None Declared

PenDA, a rank-based method for Personalized Differential Analysis: application to lung cancer

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Secondary topic : Methodological developments for Systems Biology

Your abstract : Since the recent development of high-throughput sequencing technologies, differential analysis has focused on characterizing the genetic, transcriptomic or epigenetic changes between groups of samples. However these studies identify genes or loci that are significantly modified *in average* between two conditions but often neglect to quantify differences at the *individual* level. Current analysis tools are not designed to accurately perform personalized differential analysis. Such methods will allow to explore patient-specific patterns of deregulation and to provide a comprehensive analysis of the deregulation landscape associated with heterogeneous disorders such as cancer.
With PenDA, we propose an original rank-based statistical method to perform personalized differential analysis in hundreds of samples. For each tested case, the method identifies the deregulated genes/probes as referred to the control group. We evaluated the method on both simulated and biological datasets. We applied the method to The Cancer Genome Atlas (TCGA) lung cancer RNA-seq dataset. Clustering by personalized differential analysis identified clinically meaningful clusters of patients with significant decrease in 10-year survival probabilities. We also provide an R package that ensures reproducibility of the methods and allows to easily analyze any dataset provided by the user.
We expect this method to have a significant impact on the characterization of the molecular signature of each tumor at the individual level, which would lead to the identification of prognosis markers towards the development of personalized medicine strategies such as anti-cancer therapies.

Disclosure of Interest: None Declared

A hormone-regulated translatome in primary cells highlights a positive feedback loop of signaling components operating at the level of translation

Aurélie Tréfier[1], Thomas Bourquard[1], Kelly León[1], Astrid Musnier[1], Julia Morales[2], Thomas Boulo[1], Hamza Ouchène[1], Rémi Coulaud[1, 1], Valérie Labas[3], Lucie Combes-Soia[1], Florian Guillou[1], Eric Reiter[1], Anne Poupon[3], Pascale Crépieux[* 3], Romain Yvinec[1]
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Secondary topic : Modelling Networks and Circuits
Your abstract : Regulatory mechanisms acting at the level of translation allow the cell to respond in a few minutes to subtle changes in the extracellular *milieu*. For example, Follicle-Stimulating Hormone(FSH) binding to the Follicle-Stimulating Hormone Receptor (FSHR) targets mRNA-specific translation tofine-tune Sertoli cell protein content in the male gonad. The FSHR is a G protein-coupled receptor(GPCR). Through a complex signaling network, GPCRs indirectly regulate gene transcription, but little is known about their role in mRNA translation. Here, we used polysome profiling and RNA sequencing to identify the FSHR-regulated translatome in rat primary Sertoli cells. In a relatively short time period (90 minutes), only dozens of gene were found to be regulated at the transcriptional level, while more than two thousand mRNA were regulated at the translational level. Importantly, the translation of many of them into a protein was validated by parallel label-free mass spectrometry. Several well-known testis markers were identified in these translated mRNAs. Importantly, network inference based on the translatome dataset suggested that many components belonging to the major FSHR-dependent signaling pathways (Gαs, cAMP) may be co-translated in response to FSH. Independent sets of experiments have confirmed this point.
In conclusion, by reporting one of a few GPCR-dependent translatomes analyzed at the systems level, our data highlight a potential positive feedback loop of FSH-dependent signaling component at the level of translation.We expect that this translatome will eventually provide insights onto the molecular mechanisms whereby this class of receptor physiologically controls cell phenotype.

Disclosure of Interest: None Declared

Systems Medicine A
MONDAY, OCTOBER 29 – 10:50 AM – 12:30 PM

Large-scale analysis of human gene expression variability associates highly variable drug targets with lower drug effectiveness and safety

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Secondary topic : Methodological developments for Systems Biology

Your abstract : The effectiveness of drugs tends to vary between patients. One of the well-known reasons for this phenomenon is genetic polymorphisms in drug target genes among patients. We propose that differences in expression levels of drug target genes across individuals can also contribute to this phenomenon.

To explore this hypothesis, we analyzed the expression variability of protein-coding genes, and particularly drug target genes, across individuals. For this, we developed a novel variability measure, termed Local Coefficient of Variation (LCV), which ranks the expression variability of each gene relative to genes with similar expression levels. Unlike commonly used methods, LCV neutralizes expression levels biases without imposing any distribution over the variation.

Application of LCV to RNA-sequencing profiles of 19 human tissues and to target genes of 1,076 approved drugs revealed that drug target genes were significantly more variable than protein-coding genes. Analysis of 113 drugs with available effectiveness scores showed that drugs targeting highly-variable genes tended to be less effective in the population. Furthermore, comparison of approved drugs to drugs that were withdrawn from the market showed that withdrawn drugs targeted significantly more variable genes than approved drugs. Lastly, upon analyzing gender differences we found that the variability of drug target genes was similar between men and women.

Altogether, our results suggest that expression variability of drug target genes could contribute to the variable responsiveness and effectiveness of drugs, and is worth considering during drug treatment and development.

Disclosure of Interest: None Declared

Mathematical modelling of E2F1 repression by cooperative microRNA pairs in the context of anticancer chemotherapy resistance

Xin Lai[* 1], Shailendra Gupta[2], Ulf Schmitz[3], Stephan Marquardt[4], Susanne Knoll[4], Alf Spitschak[4], Olaf Wolkenhauer[2], Brigitte Pützer[4], Julio Vera[1]
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Secondary topic : Systems Medicine

Your abstract : High rates of lethal outcome in tumour metastasis are associated with the acquisition of invasiveness and chemoresistance. Several clinical studies indicate that E2F1 overexpression across high-grade tumours culminates in unfavourable prognosis and chemoresistance in patients. Thus, fine-tuning the expression of E2F1 could be a promising approach for treating patients showing chemoresistance.
We integrated bioinformatics, structural and kinetic modelling, and experiments to study cooperative regulation of E2F1 by microRNA (miRNA) pairs in the context of anticancer chemotherapy resistance. We showed that an enhanced E2F1 repression efficiency can be achieved in chemoresistant tumour cells through two cooperating miRNAs. Sequence and structural information were used to identify potential miRNA pairs that can form tertiary structures with E2F1 mRNA. We then employed molecular dynamics simulations to show that among the identified triplexes, miR-205-5p and miR-342-3p can form the most stable triplex with E2F1 mRNA. A mathematical model simulating the E2F1 regulation by the cooperative miRNAs predicted enhanced E2F1 repression, a feature that was verified by in vitro experiments. Finally, we integrated this cooperative miRNA regulation into a more comprehensive network to account for E2F1-related chemoresistance in tumour cells. The network model simulations and experimental data indicate the ability of enhanced expression of both miR-205-5p and miR-342-3p to decrease tumour chemoresistance by cooperatively repressing E2F1. Our results suggest that pairs of cooperating miRNAs could be used as potential RNA therapeutics to reduce E2F1-related chemoresistance.

Disclosure of Interest: None Declared

Controllability analysis of the core gene regulatory network underlying epithelial-to-mesenchymal transition in the context of epithelial cancer

Eduardo CHAIREZ-VELOZ[1], José Luis CALDU-PRIMO[2], José DAVILA-VELDERRAIN[3], Alberto SORIA-LÓPEZ[1], Elena R ALVAREZ-BUYLLA[4], Juan Carlos MARTINEZ-GARCIA[* 1]
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Secondary topic : Modelling Networks and Circuits

Your abstract : As a complex developmental process, Epithelial-to-mesenchymal transition (EMT) is involved in morphogenesis, tissue regeneration and cancer progression. This dynamical process is characterized by a series of cell-state transitions, in which belonging to epithelial tissue loose their epithelial characteristics, and gain mesenchymal properties (e.g., increasing motility). Therefore, some experimentally grounded gene regulatory networks (GRNs) models have started to be proposed to uncover the EMT regulatory core, and thus contribute to the understanding of the EMT regulation and to guide experiments by generating testable hypotheses. Nevertheless, systematic analysis that elucidate the specific role that the involved genes (acquired by their collaboration in the network), play in transitioning not only between the two cell states, but also among intermediate states, are still very scarce. In attempt to contribute in such a need, we propose an analytical procedure based on algebraic approaches and built around Semi-Tensor Product approach (STP). We illustrate the procedure through the exploration of the structural controllability properties of the low-dimensional Boolean GRN underlying the immortalization of epithelial cells, which recovers the specific gene expression profiles that correspond to the epithelial, senescent, and mesenchymal stem-like phenotypes. Our findings suggest that there exist 9 different inducible transitions between the three main phenotypes, by a suitable external Boolean input connected to a particular gene of the network. These transitions are tested both in the Boolean and in its approximated continuous model. In addition, we found that the computed controllability matrix associated to the aforementioned EMT-GRN, provide relevant information that concerns the perturbations that give rise to some intermediate states, since its entries indicate whether the i-state (any possible gene activation configuration) is reachable from the j-state, under a set of admissible Boolean inputs. Finally, we discuss this data from a biological perspective, and we concluded that controllability analysis can give us insights on the role of the genes in the context of the network as a whole. This is particularly important when tackling EMT dynamics associated to the onset and progression of cell-state trajectories involved in disease.

Disclosure of Interest: None Declared

Patient-specific modelling of the network dynamics induced by chemotherapeutic drugs in primary and relapsed tumours

Dirk Fey[* 1], David R Croucher[2], Axel Kuehn[1, 3], Laura Tuffery[1], Franziska Elsaesser[1, 4], Sarah Robert[1, 5], Melinda Halasz[1], Boris N Kholodenko[1], Walter Kolch[1]
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Secondary topic : Modelling Networks and Circuits
Your abstract :

Nearly all aspects of cancer pathophysiology, including cancer initiation, development, progression and metastasis are driven by the dysregulation of one or more signalling networks [1]. These signalling networks consist of sets of genes that are dynamically organised. In response to a perturbation the activity of the network changes over time. In this way, signalling networks exert finely tuned control over cell fate decisions that ultimately determine the behaviour of cancer cells [2]. However, we barely understand how these dynamic activation patterns are shaped by differences between cells and patients: How does cell-to-cell variability affect drug responses? How does the genomic background of patients affect the network's input/output behaviour?

Here, I will address these questions focusing on the on the dynamic signalling network that is activated in response to chemotherapeutical drugs, and in particular the interconnected JNK/p53/BRCA1 stress-, DNA-damage response, and DNA-damage repair network in neuroblastoma, breast- and ovarian cancer. Firstly, I will present a generally applicable method for integrating static cancer-cell and tumour-profiling data into patient-specific dynamic models of cancer signalling [3]. Secondly, I will show how dynamic modelling of the JNK/p53/BRCA1 response network can explain drug-sensitivity data in a large panel of cancer cell-lines from the GDSC database. Thirdly, I will show how these patient-specific models can be used to stratify neuroblastoma patients (n=688 patients, 7 matched primary and relapsed tumours). These patient-specific simulations did not only outperform the currently used biomarkers, but also revealed deep insight into the disease mechanisms [2]. Last but not least, I will present our progress on modelling the cell-to-cell variability during the development of drug resistance. Both our theoretical and experimental results indicate that so-called cell-ensemble modelling can be used model the selective pressure of chemotherapy on cancer cells and the emergence of drug-tolerant populations.

1. Kolch, W and D Fey, *Personalized Computational Models as Biomarkers.* J Pers Med, 2017. **7**(3).
2. Fey, D, et al., *Signaling pathway models as biomarkers: Patient-specific simulations of JNK activity predict the survival of neuroblastoma patients.* Sci Signal, 2015. **8**(408):ra130.
3. Fey, D, A Kuehn, and BN Kholodenko, *On the personalised modelling of cancer signalling.* IFAC-PapersOnLine, 2016. **49**(26):312-317

Disclosure of Interest: None Declared

Optimizing drug combinations for cancer treatment using integrative network modelling

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Secondary topic : Modelling Networks and Circuits

Your abstract : The advent of targeted drugs, such as kinase inhibitors, has revolutionized cancer treatment; yet resistance to these drugs as monotherapies remains a major problem preventing their full clinical impact. Such resistance is caused in part by the ability of cancer signalling networks to adapt and rewire in response to single-drug treatment, ultimately evading the drug effect. Consequently, combination therapies are being actively investigated in multiple cancers, in order to defeat resistance associated with single agents and achieve durable response. However, given the number of possible target (drug) combinations are vast but clinical trials are slow and expensive: "How can we rationally predict and prioritize the most optimal drug combinations?" The plasticity of cancer signaling networks further suggests that well-designed *sequential* drug combinations, where the first drug 'primes' the target network for inhibition by the second drug, may be superior than *concurrent* combinations where both drugs are administered at the same time. However, "under which contexts such sequential combination therapies may be favored?"

I will first demonstrate how mechanistic dynamic modelling in conjunction with wet-lab experiments can address the 1st question. This integrative approach enabled us to predict and prioritize synergistic drug combinations targeting a multi-pathway Receptor Tyrosine Kinase signaling network in triple-negative breast cancer (TNBC), an aggressive form of breast cancer with no current targeted treatment. Validation of model predictions in TNBC cell lines and xenograft models identified a potent combination therapy for this disease, supporting the power of this approach. Moreover, analysis of TNBC clinical data and patient-specific model simulations allowed us to stratify the patients and define a subgroup that is most likely to benefit from the combined treatment. In addressing the 2nd question, I will present new results where we have developed a computational framework to identify, among thousands of possible network topologies, those conferring better sensitivity to sequential over concurrent drug combinations. Despite the diversity of possible biochemical networks, this analysis yields a design table highlighting a finite set of circuits susceptible to sequential treatments that are highly enriched with negative feedback loops. These design rules provide a useful framework to guide future application of sequential targeted therapies.

Disclosure of Interest: None Declared

Quantitative Systems Physiology
TUESDAY, OCTOBER 30 – 10:50 AM – 12:30 PM

What causes metabolic oscillations in the eukaryotic cell?

Vakil Takhaveev[*] [1], Serdar Ozsezen[1], Athanasios Litsios[1], Alexandros Papagiannakis[1], Matthias Heinemann[1]
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Secondary topic : Single-cell Systems Biology

Your abstract : Single budding yeast cells display oscillations of NAD(P)H level orbiting in unison with the cell cycle or in the absence of it. These metabolic oscillations exist in diverse growth conditions, likely reflecting a universal behavior of the living cell.
It was previously suggested that the metabolic oscillations result from the cycles of carbon-storage accumulation/liquidation or periodic mitochondrial activity. Nevertheless, we find that the metabolic oscillations persist when we disrupt carbon-storage metabolism and also in cells with impaired mitochondrial respiration. Instead, we hypothesize that a temporal separation in the synthesis of major biomass constituents causes metabolic oscillations. Specifically, the synthesis rate of at least one biomass component may change periodically. Consequently, a timely demand for building blocks and energy may cause oscillations in primary metabolism.
To test this hypothesis, we use fluorescence microscopy and microfluidics. We continuously observe NAD(P)H signal in single cells during steady growth and when the synthesis pathways of major biomass components are dynamically perturbed. Consistently with our hypothesis, we witness the metabolic oscillations inhibited shortly after blocking protein and lipid biosyntheses. We find a significant correlation between the cell cycle phase at which the perturbation is applied and the effect on the metabolic oscillations. Overall, we are able to map at which phases of the cell cycle or the metabolic oscillator protein and lipid biosyntheses are active.
To infer dynamic behavior of primary metabolic pathways that provide biomass precursors, we estimate the metabolic fluxes during the cell cycle via a thermodynamically constrained stoichiometric model. The dynamic flux map of primary metabolism is validated with perturbations of specific pathways.
This work indicates that macromolecular synthesis is likely not constant, but oscillates in unison with the metabolic/cell cycle. Especially the activity of global protein and lipid syntheses appears to change. Here, we provide a detailed view on the dynamics of fundamental biosynthetic processes and primary metabolism during the eukaryotic cell cycle.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 642738.

Disclosure of Interest: None Declared

Stochasticity of cellular growth: sources, propagation and consequences

Philipp Thomas[1], Guillaume Terradot[2], Vincent Danos[3], Andrea Weisse[*4]
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Secondary topic : Single-cell Systems Biology

Your abstract : Cellular growth displays substantial heterogeneity. In single cells, growth fluctuates over time, which ultimately can lead to significant variation across populations of cells. And because growth takes such a central role within the cell, its heterogeneity can impact a range of phenotypic responses. Identifying the sources of fluctuations in growth and how they propagate across the cellular machinery can therefore unravel important mechanisms that underpin cellular decisions.

Here we present a stochastic model to predict growth dynamics in single bacterial cells. The model expands on a mechanistic description that partitions the proteome into physiologically relevant components and considers their interplay via core cellular processes (Weisse et al, PNAS 2015). It complements the latter with stochastic dynamics and links them with dynamics of DNA replication and cell division. We accompany our model with a novel framework that enables analysis of a broad class of stochastic chemical reactions coupled with cell divisions, and moreover, efficient parameter estimation for the same class of models.

We show that our stochastic cell model accurately recovers several population-averaged data on the growth-dependence of cellular physiology in bacteria. Its predictions are further in excellent quantitative agreement with how growth fluctuations in single cells change across different growth conditions. We identify the processes responsible for this heterogeneity, and by visualising cross-correlations, we can further determine how fluctuations in these processes propagate to growth rate and then affect other cell processes. Finally, we study antibiotic responses and find that complex drug-nutrient interactions can both enhance and suppress growth heterogeneity.

Our results provide a predictive framework to integrate single-cell and bulk data and draw testable predictions with implications for antibiotic tolerance, evolutionary biology and synthetic biology.

Disclosure of Interest: None Declared

Interplay of local and global regulators in pectin catabolism during plant infection by Dickeya dadantii.

Shiny Martis B[*1], Sam MEYER[1], William NASSER[1], Michel DROUX[1], Sylvie REVERCHON[1]
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Secondary topic : Modelling Networks and Circuits

Your abstract : pel genes are the major virulence factors in Dickeya dadantii, which infects plants causing significant crop loss around the world. The Pel enzymes act by degrading pectin, which is a key source of carbon for the bacterium during plant infection. The efficient and timely expression of pels is thus tightly coupled to the cell metabolism, and this dynamical coupling is crucial in the infection process. In this study, we develop a dynamic modeling of this process, based on quantitative experimental measurements of the main molecular actors in live cells along bacterial growth, especially KDG(2-Keto-3-deoxy-gluconate) the main metabolic product of pectin degradation. Previous studies proposed the KdgR repressor to be the main regulator of these genes. When pectin is degraded into KDG, the latter binds KdgR and relieves the repression, triggering a loop of Pel production. However, our measurements demonstrate that the peak of KDG concentrations in the cell occurs considerably earlier than pel expression peaks, which cannot be explained by the dynamics of pectin catabolism mediated by KdgR alone. Instead, we are able to reproduce all observed features in a quantitative modeling where pel genes are regulated by the global regulator CRP(cAMP receptor protein) in addition to the repressor KdgR. The model was mostly parametrized from in vitro calibration experiments and describes the process at local (gene expression) as well as global (cell physiology) scale within a single framework. While pectin degradation relieves the repression of the pel genes already during the early stages of growth, the peak of expression is triggered only at the transition to stationary phase, as a result of a change in global metabolic state of the cell. This timing of expression is mainly controlled by CRP, and may reflect an anticipation strategy for further availability of pectin as the carbon source during the invasion of the pathogens in host plants. Altogether, we learn that the dynamics of infection is regulated by the physiological state of the cell through the combined action of global and specific transcriptional regulators. The model developed is one of the first to incorporate the simultaneous action of transcription factors and physiological state of the cell to model bacterial infection dynamics in a quantitative manner. It could be adapted to several human pathogens, where virulence genes are shown to be regulated by CRP in addition to more specific transcription factors.

Disclosure of Interest: None Declared

Circadian regulation of cell size, division timing and growth in cyanobacteria

Bruno Martins[* 1], Amy Tooke[2], Philipp Thomas[3], James Locke[1]
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Your abstract: When and at what size to divide are critical decisions, requiring cells to integrate internal and external cues. How cells maintain their size has been extensively studied under constant conditions. In the wild, however, cells rarely experience constant environments. For photosynthetic organisms, the pattern of daily fluctuations of sunlight is the most important environmental signal. These organisms evolved circadian clocks to anticipate daylight cycles and synchronise cellular processes. Here, we examine how the 24-hour circadian clock and environmental cycles modulate cell size control and division timings in the cyanobacterium *Synechococcus elongatus* using single-cell time-lapse microscopy. Under constant light, wild type cells follow an apparent sizer-like principle. Closer inspection reveals, however, that the clock generates two distinct subpopulations, with cells born in the subjective day following different division rules from cells born in subjective night. A stochastic model explains how this behaviour emerges from the interaction of cell size control with the clock. Using Bayesian inference, we obtain a coupling function that describes how the clock affects the division rate throughout the 24-h day. We demonstrate that the clock continuously modulates the probability of cell division throughout day and night, rather than solely applying an on-off gate to division as the current paradigm proposes. Iterating between modelling and experiments, we go on to show that the combined effects of the environment and the clock on cell division are explained by an effective coupling function. This effective function incorporates both the effect of the clock and the time-dependent growth rate imposed by the environment. Under naturally graded light-dark cycles, this effective coupling shifts cell division away from dusk and dawn, when light levels are low and cell growth is reduced. Our analysis allows us to disentangle, and predict the effects of, the complex interactions between the environment, clock, cell size control, and cell growth.

Disclosure of Interest: None Declared

Single-cell Systems Biology
TUESDAY, OCTOBER 30 – 10:50 AM – 12:30 PM

Noise and correlated gene expression in a one-dimensional organism

Rinat Arbel-Goren[*1], Leora Schein-Lubomirsky[1], Antonia Herrero[2], Enrique Flores[2], Joel Stavans[1]
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Secondary topic : Developmental Systems Biology

Your abstract : Cells having the same genetic information can behave very differently due to variations in molecular species numbers -noise- caused by inevitable stochastic fluctuations in gene expression. How do cells in multicellular organisms achieve high precision in their developmental fate in the presence of noise? We address this fundamental question from a Systems Biology perspective focusing on *Anabaena* cyanobacterial filaments as a model system. Under nitrogen-rich conditions all cells are vegetative. However, under nitrogen deprivation, filaments form one-dimensional, patterns of single nitrogen-fixing cells, separated by nearly-regular intervals of photosynthetic, vegetative cells. Here we study the statistics of fluctuations of gene expression in the production of HetR, a transcription factor essential for heterocyst differentiation, in the undifferentiated state (nitrogen-rich conditions). Using a chromosomal P_{hetR}-*gfp* fusion, we measure fluorescence in individual cells in wild-type and mutant backgrounds to demonstrate that expression fluctuations of *hetR* in nearby cells are coupled, with a characteristic spatial range of two to three cells, setting the scale for cellular interactions along a filament. Correlations between cells arise predominantly from intercellular molecular transfer. Our analysis shows that the septal protein SepJ may be implicated in the cell-cell transfer of the PatS-derived inhibitor of HetR, highlights differences between septal proteins and brings out the role of HetR positive autoregulation. By following fluctuations in the same cells over time, we calculate the temporal autocorrelation of the fluctuations and show that the timescales of their decay under rich and poor nitrogen conditions scale with the cell doubling time. Overall, our statistical analysis of primordial fluctuations illuminates the fundamental role that positive feedback, lateral inhibition, cell-cell communication and noise play in the developmental program.

Disclosure of Interest: None Declared

Experimental and theoretical study of nuclear diffusion dynamics of transcription factors

Nacho Molina[*1]

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Secondary topic : Multi-omics

Your abstract : Gene expression is regulated by transcription factors (TFs) that recognize specific regulatory DNA sequences. The search strategies that TFs use to find these regulatory target sites are key to understand the dynamics of transcriptional regulation. The standard kinetic model assumes a 3D plus 1D diffusion process: TFs either move freely in solution or slide on DNA. This simple model gives an elegant explanation of why the TF-DNA association rate measured in-vitro is 100 times faster than the rate expected based only on 3D diffusion. However, recent single-molecule experiments in-vivo have suggested that the 3D structure of chromatin influences the diffusion process.

We developed a novel multi-scale stochastic model that integrates DNA-protein interaction with high-resolution information on the 3D structure of chromatin. The dynamics of TFs is modeled as a slide plus jump diffusion process on a chromatin network constructed from high-resolution Hi-C data. Our analysis allows to uncover the effects of chromatin structure on the diffusion process and provides genome-wide testable predictions for the occupancy profiles of TFs and target search times. In particular, we show that the search time is determined by three factors: the average residence time, the effective TF concentration and the number of local chromatin contacts. Furthermore, we showed that binding sites clustered on a small number of topological associated domains leading to a higher local concentration of TFs. Importantly, this result suggests that recent observations showing an inhomogeneous nuclear concentration of Sox2 in ES cells may be a common feature of TFs. Moreover, it supports the hypothesis that chromatin structure helps to compartmentalize the nucleus creating nanoreactors and thus increasing the efficiency of biochemical reactions.

Furthermore, using fluorescence loss in photobleaching (FLIP) and stochastic modelling we studied the diffusion dynamics of key regulatory factors for stemness maintenance and cell differentiation. We estimated effective diffusion rates across the nucleus and during different phases of the cell-cycle. Our approach allowed us to study how different condensation states of chromatin influence the diffusion dynamics of transcription factors and its implications on gene regulation.

Disclosure of Interest: None Declared

Cell-to-cell variability in the activation of the Heat Shock Response

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Secondary topic : Modelling Networks and Circuits

Your abstract : In mammalian cells, environmental (oxidative, heat) stress induces the Heat Shock Response (HSR) activation, leading to an increase of Heat Shock Proteins (HSPs) to maintain proteostasis. The Heat Shock Factor 1 (HSF1) transcription factor plays a key role in the detection of the stress as well as in the HSR regulation. While the HSR has been widely investigated, very little is known about its cell-to-cell variability. Even for a monoclonal population of cells all exposed to the same hyperthermic stress, several distinct cellular fates can be observed (cell death, survival, ...).
In the present work, we address the following questions :
– What are the key dynamic components describing the HSR at several time scales ?
– How to monitor, analyze, and understand the cell-to-cell variability in HSR of a monoclonal cell line ?
Under different stressful conditions, HSF1 forms a small number of highly dynamic structures as the so-called Nuclear Stress Bodies (nSBs) that offer an exciting readout of the cellular responses at the single cell level. From time lapse imaging of HSF1, the activation/deactivation of HSR was monitored at the level of single HeLa cells at various temperature (41°C-44°C).
Surprisingly, while the averages of nSB dynamics over the cell population at a given temperature is similar to biochemically established time traces of HSF1-HSE binding, (i) even for long hypertermic exposure (3 hours) only a subset of the cells exhibit an HSF1 activation, and (ii) the dynamics of HSF1 activation vary greatly among the responding cells. To gain a better description of the HSR dynamics, a data driven mathematical description of HSR network was built, highlighting the titration of HSF1 by chaperons as the guiding line of a regulation network describing the HSR at both the population and single cell levels. The cell-to-cell variability was then investigated by statistical analysis and network parameters sensitivity analysis, identifying HSF1 and HSPs initial protein pool as best candidates responsible for the variability.

Disclosure of Interest: None Declared

Spatially distributed network between EGFR and phosphatases optimizes growth factor sensing at criticality

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Secondary topic : Modelling Networks and Circuits

Your abstract : The proto-oncogenic epidermal growth factor receptor (EGFR) is a tyrosine kinase whose sensitivity to growth factors and signal duration determines cellular behavior. We resolve how the phosphorylation response of EGFR to epidermal growth factor originates from dynamically established recursive interactions with protein tyrosine phosphatases (PTPs). Using advanced single cell microscopy techniques and dynamical systems theory we first identified which are the major EGFR dephosphorylating activities. We then revealed how vesicular recycling of EGFR unifies the interactions with these PTPs that are localized on distinct membranes to generate a spatially distributed network architecture that dictates how cells sense and respond to time varying growth factor signals. These signal processing characteristics result from the intrinsic organization of the network close to a critical region in parameter space where only a single steady state, the basal EGFR phosphorylation is stable. We therefore propose a novel concept of information processing with metastable states at criticality and demonstrate how this allows the system to translate and interpret the information about the changing environment.

1. A. Stanoev, A. Mhamane et al., / A. Koseska*, P. Bastiaens*, (2018) Interdependence between EGFR and phosphatases spatially established by vesicular dynamics generates a growth factor sensing and responding network. Cell Systems, in press.

Disclosure of Interest: None Declared

Integration of GDF11 and TGF- β on the SMAD-signaling pathway - modelling population average and variability based on single cell data

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Secondary topic : Single-cell Systems Biology

Your abstract : GDF11 and TGF-β are two members of the TGF-β superfamily and are involved in regulation of differentiation and cell growth in embryonic tissues, but also in homeostasis and regeneration in adult tissues and hence are important players of cellular development and homeostasis. Alterations in the cellular response to TGF-β is also involved in severe human diseases such as cancer. Both ligands interact with a conserved family of cell surface specific protein kinase receptors generating intracellular signals using the common SMAD-signaling pathway: Phosphorylation of the cytoplasmic signaling molecules (by ligand-specifc TGF-β/activin receptors) induces partnering with the signaling transducer SMAD4 which in turn induces translocation of SMAD complexes to the nucleus where it partners with transcription factors resulting in cell-state specific modulation of transcription of target genes.
Our aim is to investigate how inputs from different receptors sharing a common signaling pathway interact with each other and how ligand-specific responses are encoded. Furthermore, we wish to understand the mechanisms of stable information transmission from the extracellular medium to the nucleus despite intracellular noise. We acquired quantitative time-resolved measurements at the single-cell level by combining live-cell imaging of fluorescent SMAD fusion proteins with automated image analyses to compare the long-term signaling dynamics in thousands of individual cells. Based on stimulation experiments with TGF-β and/or GDF11, we calibrate an ordinary differential equation-model that describes the dynamics of SMAD transcription factor complex translocation from the cytoplasm to the nucleus. Using distinct parameter sets, we describe subpopulations of cells showing qualitatively distinct dynamic responses according to time course clusters in the data. We found that ligand-specific responses can be described by mechanistic modeling of the TGF-β and GDF11 receptor complexes, both of which are connected to a shared SMAD module. Surprisingly, the two ligands were characterized by distinct mechanisms of signal termination at the population-average level and also showed specific footprints of cellular heterogeneity in the SMAD signaling output.
Our analyses shed further light on the mechanisms of robust and specific information transmission in the SMAD signaling pathway.

Disclosure of Interest: None Declared

Systems Biology for Synthetic Biology
TUESDAY, OCTOBER 30 – 10:50AM – 12:30 PM

An artificial cell-cycle system: how network structures modulate the clock functions

Qiong Yang[*1]
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Secondary topic : Modelling Networks and Circuits

Your abstract : Although central architectures drive robust oscillations, networks containing the same core vary drastically in their potential to oscillate. What peripheral structures contribute to the variation of the oscillator behaviors remain elusive. We computationally generate an atlas of oscillators and systematically analyzed robustness of all oscillatory topologies. We found that, while certain core topologies are essential for robust oscillations, local structures substantially modulate the degree of robustness. Strikingly, two key local structures, incoherent inputs and coherent inputs, can modify a core topology to promote and attenuate its robustness, additively [1]. These findings underscore the importance of local modifications besides robust cores, which explain why auxiliary structures not required for oscillation are evolutionarily conserved. It also suggests a convenient way to design robust synthetic circuits. We now extend this computational framework to the study of broader biological clock functions like tunability, i.e. the extent to which a clock can be tuned in frequency.
Experimentally, we developed an artificial cell-cycle system to mimic the real mitotic oscillatory processes in microfluidic droplets [2]. The artificial cells are adjustable in sizes and periods and can perform self-sustained oscillations for many cycles over multiple days. Moreover, the system can not only reconstitute a simple cytoplasmic-only mitotic circuit, but also can successfully drive the periodic progression of a series of downstream mitotic events that self-organize in time and space, including chromosome condensation, nuclear envelope breakdown, to mimic real mitotic cells. The oscillation profiles such as period and number of cycles can be reliably tuned by the amount of clock regulators or sizes of droplets. Such innate flexibility makes it key to studying clock functions of tunability and stochasticity at the single-cell level. With nanofabrication and long-term time-lapse fluorescence microscopy, this system enables a high-throughput, single-cell analysis of clock dynamics and functions. We now combine this experimental platform with mathematical modeling to elucidate the topology-function relation of biological clocks. Specifically, we ask how network structures are linked to the essential functions of early embryonic cell cycles, such as tunability and robustness.
[1]Z. Li, S. Liu, and Q. Yang (2017). Cell Systems 5, 72.
[2]Y. Guan et al (2018) eLife 7, e33549.

Disclosure of Interest: None Declared

On the feasibility of complex synthetic biological circuits

Carlos Toscano-Ochoa[*1], Jordi Garcia-Ojalvo[1] and Dynamical Systems Biology
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Secondary topic : Modelling Networks and Circuits

Your abstract : The implementation of a biological computer has been one of the most remarkable challenges in the field of biotechnology in the last few decades. All kinds of logic gates have been developed to work in bacteria and eukaryotes. This has allowed to design several circuits with minimal complexity. However, soon it was evident that an arbitrary complex circuit requires the distribution of its components among different types of cells that communicate between them. This communication is what we call a wire. So far, we know that a circuit implementation without spatial segregation would be virtually impossible if the numbers of wires is too high, so now the scientific community is moving towards the spatial segregation of the circuit. Nevertheless, not so much effort has being paid to solving the wiring problem, and to measuring the actual limitations of the wires themselves. Here we show a very simple model for non-growing cells connected through a wire that is able to predict the behaviour of the system. We also explore the logic capabilities of a wire and show that these capabilities are compatible with the wire acting as a buffer. Finally, we show that a system of several cell types connected through wires can work as intended if and only if an algebraic system of conditions in the form of linear inequalities is obeyed. In summary, the feasibility of a complex biological circuit is equivalent to the solution of a linear programming problem.

Disclosure of Interest: None Declared

Perceptions of inherent safety: a comparison study from the bioengineering field

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Your abstract: Perceptions of Inherent Safety: A Comparison Study from the Bioengineering Field

Because of rapid developments within the field of biotechnology, uncertainties rise with regard to their potential risks and how to assess and manage these. Based on these rising uncertainties, the process of policymaking needs to be modernised. Currently, people in the bioengineering field are considering incorporating concerns of safety explicitly throughout every step of the biotechnology innovation chain. This paper reflects on findings how different actors along this innovation chain perceive the concepts of 'risk', 'safety' and 'inherent safety' in the field of emerging biotechnologies for industrial applications.

Concepts addressed in this paper are unravelled and analysed by means of a literature review and in-depth interviews with stakeholders from the field of industrially applied biotechnologies. These stakeholders consist, amongst others, of experts in the field of risk assessment and management, actors related to two projects that are currently being executed in the bioengineering field, and governmental actors. By means of these analyses, perceptions and interpretations of these safety concepts within the literature and in practice can become clear. This will reveal if, and to what extent these perceptions align with each other. Obtained knowledge will lead to better insight in the different interpretations of safety, risks and the distribution of accompanying responsibilities among stakeholders, enabling identification of bottlenecks in the field of governance for biotechnologies, leading to better management of possible risks.

Disclosure of Interest: None Declared

Optimization of gene expression through cost-effective promoter architectures

Dvir Schirman[*1], Yonatan Katzenelenbogen[1], Orna Dahan[1], Yitzhak Pilpel[1]
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Secondary topic : Systems Biology for Synthetic Biology

Your abstract : Gene expression is a costly process as it consumes common resources and raw materials from the cell. Regulation of gene expression is thoroughly studied, however there is still a lack of knowledge on how can cells optimize their expression costs. Meaning, reducing expression cost while maintaining a desired expression level.

A key mechanism for regulating gene expression is the promoter architecture, specifically through combination of transcription factor binding sites (TFBS). Several studies have explored the effect of promoter architecture on expression level. In this study we wish to ask whether different architectures impose different levels of burden on the cell, and reveal design principles that can help to optimize gene expression.

To reveal how combinations of different TFBS affect cost of expression, we utilize a library of ~2500 unique barcoded variants in *S.cerevisiae* expressing a reporter gene (Mogno et al. Genome Research 2013), in which promoters differ in their TFBS content. Each promoter is built from a random combination of 12 possible TFBS, upstream to a minimal basal promoter. Here we measured RNA expression and the relative fitness of each variant using independent repeats of a competition assay followed by deep sequencing.

Surprisingly, we observe no correlation between expression level, and fitness scores, possibly due to a low load of the unneeded reporter gene. Nevertheless, we observe a span of fitness scores which is consistent across independent repeats, indicating that information embedded in the promoter indeed modulates the expression cost independently from expression level.

We notice that variants which demonstrate higher fitness have less TFBS regardless of the specific transcription factor (TF) identity. Meaning, promoter architecture that includes more binding sites is less efficient, possibly due to sequestration of TFs by the synthetic promoter. To corroborate This finding, we analyzed an independent dataset (Keren et al, Cell 2016) which demonstrates the same phenomena.

Results of this study can help to unravel mechanisms that govern the economy of gene expression, and are involved in shaping the genome.

Disclosure of Interest: None Declared

Model-based design of robust synthetic biological circuits

Claude Lormeau[* 1, 2, 3], Fabian Rudolf[2], Mikołaj Rybiński[4], Jörg Stelling[2, 3]
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Secondary topic : Modelling Networks and Circuits

Your abstract : Computational methods enable the design of synthetic biological circuits demonstrating a specific dynamic behavior. Current methods rest on the assembly of parts characterized in different contexts, which often fail to operate as predicted when combined, or when they operate in a different context. Here we introduce a circuit design method that compensates for parts' uncertainty by identifying circuit topologies whose behavior is robust to variations in parameters. We first validated our method *in silico* to the well-known case study of three-node circuits able to achieve biochemical adaptation. Our heuristic topological filtering approach proved to yield efficiently hundreds of robust circuit designs in a Bayesian framework. Taking advantage of the scalability of our method, we then applied it to the real case of designing and constructing a synthetic circuit with a novel, non-intuitive behavior: a decoder that discriminates between short and long pulses of an intra- or extracellular signal. By responding to short pulses of signals only, and leaving aside the long inputs, such a decoder would enable us to multiplex endogenous pathways for synthetic biology purposes, in a way that does not hinder the natural function of the pathway. Alternatively, it could respond appropriately to, for example, physiological signals on different time-scales in future biomedical applications. Our novel approach, calibrated with our own part characterization experiments, yielded a selection of circuit topologies, biological parts and experimentally tunable conditions that are most likely to function *in vivo*. While most of the current model-based design methods focus on logical circuits, our approach could expand the scope of reliable design to more complex dynamic behaviors.

Disclosure of Interest: None Declared

Methodological developments for Systems Biology B
WEDNESDAY, OCTOBER 31 – 10:50 AM – 12:30 PM

Sensitive parameters and tipping points of biochemical networks with potential applications in precision medicine

Satya Swarup Samal[* 1], Jeyashree Krishnan[1, 2], Ali Hadizadeh Esfahani[1], Christoph Lüders[3], Andreas Weber[3], Andreas Schuppert[1], Ovidiu Radulescu[4]
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Secondary topic : Modelling Networks and Circuits

Your abstract : It has been suggested that complex human diseases can be understood by studying the effects of perturbations on the functioning of biochemical reaction networks (BRN) describing intracellular processes. In such models, inter-individual genetic and epigenetic differences impacting response to therapy, could be taken into account at the level of network mechanistic details or parameters. Additionally, due to inherent robustness of the networks, only a small number of sensitive parameters and tipping points are expected. Mathematically, such phenomena are studied with techniques from sensitivity analysis and bifurcation theory, requiring precise values of the kinetic parameters which is feasible for small networks but not for large networks as relevant for precision medicine.

In this context, we propose a novel computational approach based on tropical geometry to study the qualitative dynamical properties of BRNs that are modeled using non-linear Ordinary Differential Equations (ODEs) and parametrized by orders of magnitudes rather than precise numerical values. The main idea of our approach is to identify situations when two or several terms of different signs equilibrate each other and dominate all the remaining terms in the right-hand side of the ODEs defining the BRNs kinetics, which we refer to as tropical equilibration (TE). A typical trajectory in such ODE based kinetics consists in a succession of qualitatively different slow segments separated by faster transitions. The slow segments, generally called metastable regimes, are approximated by TEs. For a given BRN, we study the changes in TEs with respect to the perturbations in parameters and describe a score to quantify it. The benefits of our proposed approach over the extant techniques are twofold: Firstly, the method scales from medium (tens of variables and parameters) to high dimensional systems (hundreds of variables and parameters). Secondly, in addition to approximating the steady states, our method also approximates the metastable regimes, which are network collective modes that could be interpreted as steps towards disease with potential applications for diagnostics.

Using the MAPK/PI3K signaling network as an example, we test the idea that large changes of the metastable states can be associated to cancer disease specific alterations as well in the determination of putative drug targets.

Disclosure of Interest: None Declared

Parameter estimation in dynamical models for systems biology – the delicate balance between identifiability and predictivity

Anne Poupon[*1] and BIOS
[1]INRA/CNRS, Nouzilly, France

Secondary topic : Modelling Networks and Circuits
Your abstract : Parameter estimation in dynamical models for systems biology – the delicate balance between identifiability and predictivity

Topic: Methodological developments for Systems Biology

Yann Jullian[1], Thomas Bourquard[2], Mohammed Akli Ayoub[2], Romain Yvinec[2], Pascale Crépieux[2], Eric Reiter[2] & Anne Poupon[2,*]

1: CaSciModOT, UFR de Sciences et Techniques, Université François-Rabelais, F-37041 Tours, France.
2: Biology and Bioinformatics of Signaling Systems (BIOS) group, INRA, UMR85, Physiology of Reproduction and Behaviors (PRC), CNRS, UMR7247, François Rabelais University, F37041, France.
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The importance of predictive models in the discovery of new drugs, and more generally in the study and control of cellular signalling is now fully recognized. However, such models require the accurate estimation of unknown parameters. We have developed HYPE (HYbrid method for Parameter Estimation) a novel method for the estimation of unknown parameters in dynamical systems. This method is based on machine-learning algorithms and on an original, empirically-built, objective function. We have shown on toy models that HYPE allows achieving sufficient accuracy in the fitting of the model to a given set of data for the models to be predictive, as confirmed by additional data.

Using this method, we revisit our previously reported model of signalling triggered by the angiotensin receptor (Heitzler et al., Mol Syst Biol 2012). Although this model was able to correctly predict experimental data that have not been used for parameter estimation, many parameters of the optimized model are not identifiable. On this model we study how the notion of parameter identifiability can be used as a guide for model reduction. We also study the predictivity of the different sub-models and how the over-simplification of the model, that leads to a better identifiability, can also lead to a loss of predictivity.

Disclosure of Interest: None Declared

The parameter explosion problem: extending the scope of GRN modelling by combining reduced models with evolutionary computation

Ozgur Akman[*1], Khulood Alyahya[2], Kevin Doherty[2], Jonathan Fieldsend[2], Andrew Millar[3]
[1]Mathematics, [2]Computer Science, UNIVERSITY OF EXETER, Exeter, [3]SynthSys, University of Edinburgh, Edinburgh, United Kingdom

Secondary topic : Modelling Networks and Circuits

Your abstract : The gene regulatory networks (GRNs) that comprise the circadian clock modulate biological function across a range of scales, from gene expression to performance and adaptive behaviour. In recent years, computational models of these networks have become useful tools for quantifying the complex regulatory relationships underlying the clock's oscillatory dynamics. However, optimising the large parameter sets characteristic of these models places intense demands on both computational and experimental resources, and this constrains the size and complexity of models that can be constructed from data using common parameter-fitting approaches (the parameter explosion problem).

In this talk, it will be shown that combining reduced models with evolutionary computation can dramatically reduce both the parametrisation and the computational load, making the state and parameter spaces more computationally tractable. In particular, by fitting models based on Boolean logic and the S-System formalism to timeseries data using single- and multi-objective evolutionary algorithms (EAs), it will be shown that the reduced formulations can accurately reproduce the complex responses to environmental inputs generated by more biochemically detailed models. It will also be demonstrated that the EAs can be adjusted to search over alternative model architectures, thereby conferring the reduced formulations with sufficient predictive power to identify optimal regulatory structures from experimental data. Finally, it will be shown that local optima networks (LONs) – a recent innovation in landscape analysis – provide a compact means of visualising the GRN search landscape, and of quantifying key features affecting the difficulty of the search problem (*e.g.* multimodality, neutrality and deceptiveness).

This work indicates that the capacity of reduced models to provide a computationally efficient representation of system behaviour could facilitate the reverse-engineering of larger-scale biochemical networks, including multi-scale models that integrate regulatory and metabolic pathways.

Disclosure of Interest: None Declared

Hyperspectral cell sociology analysis of histological specimens

Martial Guillaud[*1,1], Calum MacAulay[1]
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Secondary topic : Multiscale Systems Biology

Your abstract : Recent advances in optics, multiplex immuno-staining, Hyperspectral Imaging and Artificial Intelligence algorithms are revolutionizing biology, medicine and more especially pathology thanks to the adoption of Whole Slide Scanner in Clinical Pathology settings. It is now possible to interrogate multiple molecules spectrally, at high resolution over the entire area of very large biopsies. These novel technologies generate unprecedented amounts of data, requiring novel approaches and quantitative tools to extract pertinent biological information from these large and hierarchical data sets.

We propose a novel approach, our ASTERICS suite, centred around the power of hyperspectral cell sociology, to ***develop, test and validate***imaging biomarkers for the diagnosis, prognosis and management of cancers. Based upon a pipeline using spectral unmixing, image segmentation, Voronoi-based mathematical modeling, hierarchical data based features extraction, deep learning algorithms, Monte-Carlo simulations, ASTERICS measures Tissue Phenotype of the samples at the cellular level (cell phenotype and DNA chromatin), the imbedded tissue architecture and cell sociology which quantifies the spatial relationship of different cell types

Three applications will be presented:

- *Multi-scale Tissue Architecture Analysis* of Prostate cancer to predict biochemical recurrence in brachytherapy patients and progression in Active Surveillance patients. Using Feulgen stained biopsies, combining measurements of the overall tissue organisation with those of within each gland, we were able to predict cancer recurrence with an accuracy of 80%.

- *Large-scale DNA Organisation* to predict Breast cancer survival (10 years of follow up) in 130 patients. We developed a LDO score, which measures the nuclear DNA chromatin organization changes, which correctly classify 85% of specimens (95 patients).

- Cell–cell spatial relationship to predict Lung Cancer recurrence. We quantified a multicolour immunohistochemistry (IHC) stain panel for the quantification of antibody expression in20 lung adenocarcinomas with at least 5 years FU for CD3, CD8, and CD79a.. Cell sociology analysis identified relationships associated with metastasis: tumour cells in non-metastatic cases had increased numbers of CD8+ cytotoxic T cell neighbours.

In the dawn of personalized medicine, ASTERICS Platform may facilitate the development and validation of diagnostic, prognostic, or predictive imaging biomarkers

Disclosure of Interest: None Declared

Dynamic single cell analysis of a cell fate decision system

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Secondary topic : Single-cell Systems Biology

Your abstract : Cell fate decisions play a key role in cellular life. Budding yeast provide a unique opportunity to understand how cells take these decisions. In the presence of a mating partner, a haploid budding yeast cells can either continue to proliferate or initiate a specific differentiation program, centered on a MAPK cascade, that will ultimately allow the fusion of two partners. To study signaling events during this process, we have developed fluorescent biosensors to quantify the dynamics of MAPK activity and protein expression in single cells.

By monitoring hundreds of fusion events using automated image analysis, we can quantify the activity of the mating pathway throughout the entire process. These data can be compared to experiments performed with exogenous pheromone, where the stimulus is tightly controlled. We could highlight the complexity of the gene expression program induced in this pathway. A single transcription factor, Ste12, controls the expression of hundreds of mating genes. However, the promoter architecture of each gene dictates the timing of its induction, allowing to regulate whether a protein will contribute to the cell fate decision or is required only for the fusion process.

Cell fate decisions play a key role in cellular life. Budding yeast provides a unique opportunity to understand how cells take these decisions. In the presence of a mating partner, a haploid cells can either continue to proliferate or initiate a specific differentiation program, centered on a MAPK cascade, that will ultimately allow the fusion of two partners. To study signaling events during this process, we have developed fluorescent biosensors to quantify the dynamics of MAPK activity and protein expression in single cells. By monitoring hundreds of fusion events using automated image analysis, we can quantify the activity of the mating pathway throughout the entire process. In addition, these data can be compared to experiments performed with exogenous pheromone, where the stimulus is tightly controlled. Using these assay, we could highlight the complexity of the gene expression program induced in this pathway. A single transcription factor, Ste12, controls the expression of hundreds of mating genes. However, the promoter architecture of each gene dictates the timing of its induction, allowing to regulate precisely when a protein is expressed during the mating process depending on its function.

Disclosure of Interest: None Declared

Methodological developments for Systems Biology C
WEDNESDAY, OCTOBER 31 – 04:00 PM – 05:40 PM

miRNA selection using miRNA network a priori showed improved reliability and identify functionally related miRNAs

Hua Ting Yao[1], Rémi Souriau[1], Rémy Jardillier[1], Florent Chatelain[2], Laurent Guyon[*1]
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Your abstract : The "omics revolution" has brought lists of genes with associated p-values. For example, list of differentially expressed genes are routinely obtained. A key question remains how to select genes for further investigation. We previously proposed a Markov Random Field model to use biological knowledge information through gene network *a priori* to favor connected hits in the selection [1]. We further extend this work and show the improved performance with miRNA datasets. First we defined a total energy, sum of an external energy function of the gene p-value and a mutual energy being strictly positive (penalization) if two neighbors have different labels (hit/non hit) on the network. The mutual energy is multiplied by beta, a parameter controlling the strength of network *a priori*. The hit/non hit label for each gene is obtained by minimizing the total energy. When beta increases, the number of hits diminishes in most cases, and only the robust and/or the connected hits in the underlying gene network remain. Beta has to be chosen between zero (no network *a priori*) and beta star (the minimum beta value for which all the genes have the same label, practically non hit). We propose three improvements: a procedure to define beta star, a normalization of the mutual energy by the network degree of each gene, and a procedure to select the gene network to further prioritize gene selection. We validate these improvements using simulated and real miRNA datasets. MiRNA datasets correspond to differential expression between cancerous and adjacent healthy tissues from Clear Cell renal biopsy tumors, from two different studies and hospitals (GSE23085 and GSE11016). The first study is used as a training dataset to select miRNAs and the second as the validation dataset and arbitrarily considered as the ground truth to further compare selections. 94 miRNAs are selected after Benjamini-Hochberg correction for multiple testing, half of which are 'false positive' (FDR = 0.50). Prioritizing the selection using a functional microRNA network reduces the selection to 58 more reliable miRNAs (FDR = 0.40), and highlights the let-7 and miR-30 families.
[1] S. Robinson et al., "Incorporating interaction networks into the determination of functionally related hit genes in genomic experiments with Markov random fields". *Bioinformatics*, *33*(14), i170-i179.

Disclosure of Interest: None Declared

Optimal part characterization with shared cellular resources

Andras Gyorgy[*1]
[1]Department of Electrical Engineering, New York University Abu Dhabi, Abu Dhabi, United Arab Emirates

Secondary topic : Modelling Networks and Circuits

Your abstract : Competition for shared cellular resources causes coupling between virtually any two components that share the same machinery (e.g., RNA polymerase, ribosomes, degradation enzymes). Without accounting for the limited availability of these shared resources, the standard model of gene expression fails to reliably predict experimental data obtained either *in vivo* or *in vitro*. As a result, both analyzing natural systems and designing/debugging synthetic gene circuits currently require the creation of vast libraries of slightly different designs. Instead of creating these libraries, computational tools and predictive models both reveal and support the development of general design principles. Therefore, part characterization must include quantification of resource sequestration so that the resulting coupling phenomenon can be taken into account when analyzing natural systems and during the systems-level design of synthetic circuits ensuring correct behavior upon interconnection of the components.

To address this issue, we recently developed a mechanistic model of gene expression explicitly modeling competition for scarce resources. In addition to accurately describing the experimental data both *in vivo* using live cells and *in vitro* using cell-free extracts, this model only depends on a handful of easily identifiable parameters with clear physical interpretation. Leveraging this mechanistic model, here we outline a procedure to select the optimal set of experiments for part characterization in systems and synthetic biology.

In particular, we first quantify the information content of candidate experiments in the presence of measurement noise. Following this, we minimize the uncertainty of parameter estimates by selecting the optimal experiments. Leveraging the analytic nature of this optimization problem, in addition to outlining how to extract the most information about unknown parameters we also reveal the role competition for shared resources plays and provide guidelines how to minimize its detrimental effects. To demonstrate the practical implications of our results, we show that it is often beneficial to counter-intuitively co-express an unknown part of interest with a known “load part”: by leveraging competition for shared resources, the systematic addition of load DNA increases the information content of experiments, thus yielding sharper parameter estimates about the unknown part.

Disclosure of Interest: None Declared

A multialgorithmic simulator for whole-cell biochemical models

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

Secondary topic : Multiscale Systems Biology

Your abstract : Whole-cell (WC) dynamical models that predict phenotype from genotype and environment are a central goal of systems biology. WC models have great potential to transform bioscience, bioengineering and, medicine.

A comprehensive WC model must thoroughly represent the biochemistry of a cell, including each species, their interactions, and their kinetics. Furthermore, to capture well-characterized processes like transcription, and poorly-characterized processes like protein folding, WC models must represent different processes with different resolution. This requires multialgorithmic simulators that co-simulate multiple biochemical processes at multiple levels of resolution, each modeled by the appropriate mathematics.

We previously build a multialgorithmic simulator for a WC model of *Mycoplasma genitalium*, and Takahashi and colleagues have developed the E-cell multialgorithmic simulator. But these simulators cannot simulate comprehensive WC models because they provide limited support for flux balance analysis (FBA), reaction rules, and parallel simulation.

To enable comprehensive WC models, we created WC-Sim, an accurate, scalable, multialgorithmic simulator. WC-Sim improves upon existing simulators in several ways:

1. WC-Sim supports multiple simulation methods, including the Stochastic Simulation Algorithm (SSA), ordinary differential equations (ODEs), and FBA. This enables WC-Sim to co-simulate noisy processes with fine resolution and slowly varying processes with coarse resolution.
2. WC-Sim interpolates discrete-time algorithms such as SSA and continuous-time algorithms such as ODE integration by sharing rates of change of the continuous models with the discrete algorithms and using the rates to estimate the population changes predicted by the continuous models. This enables WC-Sim to accurately co-simulate discrete and continuous algorithms.
3. WC-Sim employs discrete event simulation to synchronize a distributed species population and multiple independent submodels. This enables arbitrarily fine-grained synchronization between submodels. It also will enable parallel simulation of large models, including models of human cells.

WC-Sim simulates models encoded in WC-Lang, a compact schema that supports most SBML constructs. WC-Sim and WC-Lang are built in Python and available open-source at https://github.com/KarrLab. We anticipate that WC-Sim and WC-Lang will facilitate comprehensive WC models that could transform bioscience, bioengineering, and medicine.

Disclosure of Interest: None Declared

Four simple rules that are sufficient to generate the mammalian blastocyst

Silas Boye Nissen[*1], Marta Perera[2], Javier Martin Gonzalez[3], Sophie M. Morgani[2], Mogens H. Jensen[1], Kim Sneppen[1], Joshua M. Brickman[2], Ala Trusina[1]
[1]Niels Bohr Institute, [2]DanStem, [3]Transgenic Core Facility, University of Copenhagen, Copenhagen, Denmark

Your abstract : Early mammalian development is both highly regulative and self-organizing. It involves the interplay of cell position, predetermined gene regulatory networks, and environmental interactions to generate the physical arrangement of the blastocyst with precise timing. However, this process occurs in the absence of maternal information and in the presence of transcriptional stochasticity. How does the preimplantation embryo ensure robust, reproducible development in this context? It utilizes a versatile toolbox that includes complex intracellular networks coupled to cell-cell communication, segregation by differential adhesion, and apoptosis. Here, we ask whether a minimal set of developmental rules based on this toolbox is sufficient for successful blastocyst development, and to what extent these rules can explain mutant and experimental phenotypes. We implemented experimentally reported mechanisms for polarity, cell-cell signaling, adhesion, and apoptosis as a set of developmental rules in an agent-based in silico model of physically interacting cells. We find that this model quantitatively reproduces specific mutant phenotypes and provides an explanation for the emergence of heterogeneity without requiring any initial transcriptional variation. It also suggests that a fixed time point for the cells' competence of fibroblast growth factor (FGF)/extracellular signal-regulated kinase (ERK) sets an embryonic clock that enables certain scaling phenomena, a concept that we evaluate quantitatively by manipulating embryos in vitro. Based on these observations, we conclude that the minimal set of rules enables the embryo to experiment with stochastic gene expression and could provide the robustness necessary for the evolutionary diversification of the preimplantation gene regulatory network.

Disclosure of Interest: None Declared

Morpheus: a user-friendly and extensible simulation framework for declarative modelling in multiscale and multicellular systems biology

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Secondary topic : Education for Systems Biologists

Your abstract : Computational modeling is increasingly important to analyze tissue dynamics during development and disease progression. A number of software tools have been designed in order to alleviate the computational challenges in multiscale simulations of multicellular sytems, but require scientists to encode their models in an imperative programming language. Morpheus (1,2), on the other hand, as the first extensible open-source software framework for multicellular sytems that is entirely based on declarative modelling, uses the novel language MorpheusML and has since proven applicable by a much broader community, including experimentalists and trainees.
We here present how MorpheusML (3) and the open-source framework (4) allow for advanced scientific work-flows that meet today's requirements of educational use, interdisciplinary research groups and expert users. MorpheusML provides a bio-mathematical language in which symbolic identifiers in mathematical expressions describe the dynamics of and coupling between the various model components. It can represent the spatial aspects of interacting cells and follows the software design rule of separation of model from implementation. Multicellular models can be expressed in MorpheusML using the user-friendly GUI. A numerical simulation is then composed by automatic scheduling of predefined components in the simulator. Moreover, Morpheus supports simulations based on experimental data, e.g. imaged cell configurations, and offers a broad set of analysis tools to extract features right during simulation. A rich c++ API allows to extend MorpheusML and the simulator with user-tailored plugins.
Finally, we explore a generalisation of the concepts underlying MorpheusML and sketch a framework-independend approach of declarative modelling for multicellular systems that is capable of overarching multiple modelling frameworks and simulation tools, easing cross-validation and reproducibility of simulation studies.
(1) Starruß et al. Morpheus: a user-friendly modeling environment for multiscale and multicellular systems biology, Bioinformatics 30, 2014.
(2) Homepage: http://imc.zih.tu-dresden.de/wiki/morpheus
(3) Model repository: https://imc.zih.tu-dresden.de/wiki/morpheus/doku.php?id=examples:examples
(4) Open source code: https://gitlab.com/morpheus.lab/morpheus

Disclosure of Interest: None Declared

Modelling Networks and Circuits B
WEDNESDAY, OCTOBRE 31 – 10:50 AM – 12:30 PM

Instantiation of patient-specific logical models with multi-omics data allows clinical stratification of patients

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Secondary topic : Systems Medicine

Your abstract : Logical models of cancer pathways are typically built by mining the literature for relevant experimental observations. Most of the time they are generic in the sense that they are supposed to recapitulate a hypothetical universal biological functioning. As a consequence, they generally do not capture the heterogeneity of patient tumors and of their therapeutic responses. We present here a novel framework to tailor logical models to a particular biological sample like a patient's tumor. This methodology permits to compare the model simulations to individual clinical data, such as drug response and survival time.

Our approach focuses on integrating mutation data, copy number alterations (CNA), and expression data (transcriptomics or proteomics) to logical models. These data need first to be binarized or set between 0 and 1, and can then be incorporated in the logical model by modifying the activity of the node, the initial conditions or the transition rates. The use of MaBoSS, a tool that uses kinetic Monte-Carlo to perform stochastic simulations on logical models and obtain model state probabilities, allows for a semi-quantitative study of the model's phenotypes and perturbations.

As a proof of concept, we use a published generic model of cancer pathways (Fumia *et al.,* 2013) and molecular data from 1904 METABRIC breast cancer patients. For this example, we test several combinations of data incorporation and discuss that the most comprehensive METABRIC patient-specific cancer models are obtained by modifying the activity of the nodes of the logical model with mutation and CNA data and altering the transition rates with RNA expression. We conclude that these models' simulations show good results when compared to the clinical data such as patients' Nottingham prognostic index (NPI) subgrouping and survival time. We observe that two highly relevant cancer phenotypes, *Proliferation* and *Apoptosis*, exhibit different simulated probabilities across NPI subgroups: patients with low survival show highly proliferative and low apoptotic probabilities, in accordance with biological expectations.

Our approach aims to combine the mechanistic insights of logical modeling with multi-omics data integration to provide patient-relevant models. This work leads to the use of logical modeling for precision medicine and will eventually facilitate the choice of patient-specific drug treatments by physicians.

Disclosure of Interest: None Declared

Structure-based kinetic modelling reveals kinase inhibitor combinations to overcome oncogenic RAS signalling

Oleksii Rukhlenko[* 1], Fahimeh Khorsand[1], Aleksandar Krstic[1], Jan Rozanc[2, 3], Leonidas Alexopoulos[3, 4], Nora Rauch[1], Keesha Erickson[5], William Hlavacek[5], Richard Posner[6], Silvia Gómez-Coca[7], Edina Rosta[7], Cheree Fitzgibbon[1], David Matallanas[1], Jens Rauch[1], Walter Kolch[1, 8, 9], Boris Kholodenko[1, 8, 9, 10]
[1]SYSTEMS BIOLOGY IRELAND, University College Dublin, Dublin, Ireland, [2]University of Luxembourg, Luxembourg, Luxembourg, [3]ProtATonce Ltd, [4]National Technical University of Athens, Athens, Greece, [5]Theoretical Biology and Biophysics Group, Theoretical Division, Los Alamos National Laboratory, Los Alamos, [6]Department of Biological Sciences, Northern Arizona University, Flagstaff, United States, [7]Department of Chemistry, King's College London, London, United Kingdom, [8]Conway Institute of Biomolecular & Biomedical Research, [9]School of Medicine and Medical Science, University College Dublin, Dublin, Ireland, [10]Department of Pharmacology, Yale University School of Medicine, New Haven, United States

Secondary topic : Multiscale Systems Biology

Your abstract : The RAS/RAF/MEK/ERK pathway is pivotal for cell proliferation and survival and is frequently hyperactivated in tumours. Oncogenic mutations in the RAS genes are one of most frequent oncogenic mutations in cancer. Despite long effort at developing RAS inhibitors, there is still no clinically available drug. As a result, the development of inhibitors of the kinases downstream of RAS has become a hot topic in drug development.
Clinically used RAF inhibitors are ineffective in RAS-mutant tumours, enhancing homo- and heterodimerization of RAF kinases, and leading to paradoxical activation of ERK signalling. Numerous mechanisms of RAF inhibitor resistance result in enhanced RAF dimerization and cannot be overcome by existing RAF inhibitors. A way to overcome resistance is the use of inhibitor combinations, but it is unclear how the best combinations can be chosen.
Using a combined experimental and computational approach, we have built a mechanistic RAS/RAF/MEK/ERK pathway model that integrates thermodynamics and kinetics of drug-protein interactions, structural elements, post-translational modifications and cell mutational status to faithfully predict RAF inhibitor responses at the network level. Our model predicts a number of unexpected and hidden properties of network responses to different types of RAF inhibitors and makes new strides in understanding resistance to these drugs. The model suggests that synergy can emerge between Type I and Type II, as well as between Type I½ and Type II RAF inhibitors and predicts new ways of overcoming RAF inhibitor resistance in RAS mutant cells.
To test model predictions, we experimentally measured responses of MEK/ERK signalling and proliferation to different RAF inhibitor types and their combinations in melanoma cells bearing oncogenic RAS, BRAFV600E mutations, or both BRAFV600E and RAS mutations. The level of MEK and ERK phosphorylation was measured by means of Western Blot, MESOSCALE and Luminex immunoassay kits. The cellular proliferation was measured by MTS and colony formation assays. Our experimental results corroborated model predictions, showing that two RAF inhibitors ineffective on their own can robustly suppress ERK pathway when used in combination. Inhibition of oncogenic RAS signaling correlated with reduced cell proliferation and colony formation.
Our results suggest a new principle of targeting the same kinase with two structurally different inhibitors that bind to different kinase conformations.

Disclosure of Interest: O. Rukhlenko: None Declared, F. Khorsand: None Declared, A. Krstic: None Declared, J. Rozanc: None Declared, L. Alexopoulos Conflict with: L.A. is a founder of ProtaTonce, a biomarker discovery and compound assessment company., N. Rauch: None Declared, K. Erickson: None Declared, W. Hlavacek: None Declared, R. Posner: None Declared, S. Gómez-Coca: None Declared, E. Rosta: None Declared, C. Fitzgibbon: None Declared, D. Matallanas: None Declared, J.Rauch: None Declared, W. Kolch: None Declared, B. Kholodenko Conflict with: Patent application (No. 1808321.2) related to this work was filed (O.R., J.Ra, W.K. and B.K.).

Systems NMR: simultaneous quantitative monitoring of RNA, protein, and metabolite dynamics for biomolecular network analysis

Yaroslav Nikolaev[*1], Dagmar Iber[2], Paola Picotti[3], Nina Ripin[1], Martin Soste[3], Frederic Allain[1]
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Secondary topic : Multi-omics

Your abstract : Biological network dynamics are complex and involve a large number of diverse biomolecules, including most prominently RNA molecules, proteins, and metabolites. Mathematical modelling is the method of choice to understand the regulatory logic of those networks, but the approach is limited by the lack of quantitative, dynamic data. We now show that liquid-state Nuclear Magnetic Resonance spectroscopy (NMR) can address this limitation as it permits the non-destructive dynamic observation of any reaction type and soluble biomolecule class simultaneously on the same sample. We demonstrate the feasibility of this "Systems NMR" approach by implementing parallel continuous observations of distinct molecule classes (metabolites, RNA, protein) and reaction types (interactions, catalysis, conformational changes) in a reconstruction of an 8-reaction co-transcriptional RNA folding network. From a single sample we recorded 100+ observables, each resolved across 30+ time-points, and used 5 observables in a mathematical model to determine 5 reaction constants. The accuracy of the measured constants was confirmed with independent methods. Beyond the technical advance, the approach delivered novel biological insight even for this very simple network, in that it revealed an unexpected cross-talk reaction, suggesting that RNA binding of UP1 (hnRNP A1) splicing regulator can be modulated by nucleotide-tri-phosphates and unspecific RNAs. Finally, we show how NMR assays could be extended to monitor networks with dozens, potentially hundreds, of metabolite- and protein-focused reactions.
“Systems NMR” puts together the dynamic resolution of biochemistry and the multiplexing ability of “omics”. To our knowledge, no other experimental method currently permits such single-sample dynamic quantification of networks consisting of different molecule and reaction types. We therefore believe that "Systems NMR" will become a key method to enable a deeper systems-level understanding of biological network dynamics.

Disclosure of Interest: None Declared

Assigning function to natural allelic variation via dynamic modeling of gene network induction

Magali Richard[1, 2], Florent Chuffart[2], Hélène Bottin-Duplus[2], Fanny Pouyet[2], Martin Spichty[2], Etienne Fulcrand[2], Marianne Entrevan[2], Audrey Barthelaix[2], Michael Springer[3], Daniel Jost[* 1], Gael Yvert[2]
[1]TIMC-IMAG, CNRS, Université Grenoble-Alpes, Grenoble, [2]LBMC, CNRS, ENS Lyon, Lyon, France, [3]Department of Systems Biology, Harvard Medical School, Cambridge, United States

Your abstract : More and more natural DNA variants are being linked to physiological traits. Yet, understanding what differences they make on molecular regulations remains challenging. Important properties of gene regulatory networks can be captured by computational models. If model parameters can be "personalized" according to the genotype, their variation may then reveal how DNA variants operate in the network. Here, we combined experiments and computations to visualize natural alleles of the yeast GAL3 gene in a space of model parameters describing the galactose response network. Alleles altering the activation of Gal3p by galactose were discriminated from those affecting its activity (production/degradation or efficiency of the activated protein). The approach allowed us to correctly predict that a non-synonymous SNP would change the binding affinity of Gal3p with the Gal80p transcriptional repressor. Our results illustrate how personalizing gene regulatory models can be used for the mechanistic interpretation of genetic variants.
Reference: Richard et al, Mol Sys Biol, 14: e7803 (2018).

Disclosure of Interest: None Declared

Inferring gene regulatory networks using single-cell data: from mechanistic modelling to statistics

Ulysse Herbach[* 1, 2, 3], Arnaud Bonnaffoux[1, 2], Angélique Richard[1], Thibault Espinasse[3], Olivier Gandrillon[1, 2]
[1]Laboratory of Biology and Modelling of the Cell, ENS de Lyon, [2]Inria Center Grenoble Rhône-Alpes, team Dracula, Inria, [3]Institut Camille Jordan, Université Claude Bernard Lyon 1, Lyon, France

Secondary topic : Single-cell Systems Biology

Your abstract : Inferring regulatory networks from gene expression data is a longstanding question in systems biology. So far, most studies have been based on population-averaged data: now that technologies enable to observe mRNA levels in individual cells, a revolution in terms of precision, the network reconstruction problem paradoxically remains more challenging than ever. Indeed, the typical variability between cells happens to differ from a small perturbation around the population mean, revealing nontrivial stochastic features such as the fundamentally bursty nature of gene expression. It is now clear that this variability can have functional significance and should therefore not be ignored when dealing with gene network inference. Here we present a bottom-up approach to tackle this problem, starting from a mechanistic - hence stochastic - model presented in previous work [1], describing interacting genes as coupled piecewise-deterministic Markov processes. The idea is then to use the probability distribution of the overall process as a statistical likelihood: the result is a promising statistical model where stochasticity is not just noise but also contains information. By exploiting the full joint distribution of genes as provided by single-cell snapshot data [2], this approach should allow for more robust network inference in a context where the number of parameters (possible interactions) is generally much greater than the number of samples (cells).

[1] U. Herbach, A. Bonnaffoux, T. Espinasse, and O. Gandrillon. Inferring gene regulatory networks from single-cell data: a mechanistic approach. BMC Systems Biology, 11(1), 2017.
[2] A. Richard, L. Boullu, U. Herbach, A. Bonnafoux, V. Morin, E. Vallin, A. Guillemin, N. Papili Gao, R. Gunawan, J. Cosette, O. Arnaud, J.-J. Kupiec, T. Espinasse, S. Gonin-Giraud, and O. Gandrillon. Single-cell-based analysis highlights a surge in cell-to-cell molecular variability preceding irreversible commitment in a differentiation process. PLoS Biology, 14(12), 2016.

Disclosure of Interest: None Declared

Modelling Networks and Circuits C
WEDNESDAY, OCTOBRE 31 – 04:00 PM – 05:40 PM

Precise adaptation in stem cell control

Niklas Korsbo[*1], Henrik Jönsson[1]
[1]The Sainsbury Laboratory, CAMBRIDGE UNIVERSITY, Cambridge, United Kingdom

Secondary topic : Developmental Systems Biology
Your abstract : Stem cells are under tight regulatory control. In plant shoots, the continuous formation of new organs is made possible by maintaining a balance between stem cell differentiation and replenishment. This balance is thought to come from a negative feedback between CLAVATA3, expressed in the stem cells and WUSCHEL, expressed in the cells below the stem cells. Induction of CLAVATA3 reduces WUSCHEL and decreases the size of the meristem. However, the system is buffered to 10-fold changes in CLAVATA3 production rates and this is not easily explained by current models [1, 2].

Here, we propose that the signalling between the two key regulators in the stem cell network undergoes precise adaptation. Precise adaptation allows a system to filter out the average of an input and just report the recent change rate of this input. This dynamics therefore enables a separation of how a system responds to changes in input depending on what timescales this input occurs at. We explain how this is achieved by ligand-induced receptor degradation, supported from experiments [3], and we show how a minimal model is able to differentiate between short-term and long-term changes, enabling model/data agreement. We further show how precise adaptation allows for a homogeneous response of cells in a gradient of input. This can explain the homogeneity of gene expressions across spatial domins in the shoot in spite of the cell non-autonomous communication between the stem cells and the organising center via gradients of diffusive molecules.

We demonstrate that precise adaptation can have an important role in stem cell regulation, allowing for buffereing to variability within the system, and possibly be important for plants developmental adaptability to environmental changes.

References:
[1] Gruel et al. (2016), *An epidermis-driven mechanism positions and scales stem cell niches in plants.*
[2] Muller et al. (2006), *Dynamic and Compensatory Responses of Arabidopsis Shoot and Floral Meristems to CLV3 Signaling.*
[3] Nimchuck et al. (2011), *Plant Stem Cell Signaling Involves Ligand-Dependent Trafficking of the CLAVATA1 Receptor Kinase.*

Disclosure of Interest: None Declared

Automated image analysis and modeling of calcium waves in plant roots

Martin Zauser[*1], Rik Brugman[2], Janos Löffler[2], Guido Grossmann[2], Jürgen Pahle[1]
[1]Biological Information Processing Group, [2]Centre for Organismal Studies, Heidelberg University, Heidelberg, Germany

Secondary topic : Methodological developments for Systems Biology

Your abstract : Plants respond to a sudden change of environmental conditions and bacterial or fungal challenges by enhanced intracellular calcium signaling. For the model plant *Arabidopsis thaliana* it was reported that calcium signals propagate in waves through the root and show stimulus-specific signatures, if the plant is stimulated by salt or bacterial peptides. Biotic stimuli like bacteria trigger slow calcium waves with a speed lower than 10 µm/s. However, if activated by salt, calcium waves travel through the plant with a speed of around 400 µm/s. We investigate the propagation of calcium waves in response to different stimuli by quantifying intracellular calcium and simulating the wave with the help of computational models.

In a first step, we developed a computational approach for calcium wave visualization and quantification, which is capable of processing and analyzing time-lapse microscopy images of plant roots. Our algorithm automatically generates time-space diagrams (kymographs) by detecting the outline of the root and calculating the mean intensity at each position along the axis of the root. Subsequently, the kymograph is normalized with respect to the minimum and maximum intensity over time at each position along the root resulting in a distinct representation of the calcium wave named the "Crestline Plot". The Crestline Plot serves as a basis for the calculation of the starting position and starting time of the wave as well as the velocity to the tip and to the shoot.

Secondly, we created a computational model for the propagation of the calcium wave with respect to different stimuli. For the simulation of biotic stimuli we used a core model based on diffusion and calcium induced calcium release. High velocities of calcium propagation cannot be explained by this model. Therefore, we followed an approach proposed by Dubiella et al. which combines the activities of calcium signaling and reactive oxygen species (ROS) signaling. We extended this approach by explicitly considering different cell sizes in the different developmental zones, which enables us to reproduce the observed velocities. We applied the automated analysis to different datasets of high-resolution microscope images of stimulation experiments and used the results to parameterize our model and probe its dynamic behavior.

Disclosure of Interest: None Declared

Principles that govern competition or co-existence in Rho-GTPase driven polarization in the budding yeast

Jian-Geng Chiou[* 1], Samuel Remirez[2], Helen Lai[1], Trevin Zyla[1], Timothy Elston[2], Daniel Lew[1]
[1]Department of Pharmacology and Cancer Biology, Duke University, Durham, [2]Department of Pharmacology, University of North Carolina at Chapel Hill, Chapel Hill, United States

Secondary topic : Developmental Systems Biology

Your abstract : Rho-GTPases are master regulators of polarity establishment and cell morphology. Positive feedback enables concentration of Rho-GTPases into clusters at the cell cortex, from where they regulate the cytoskeleton. Different cell types reproducibly generate either one (e.g. the front of a migrating cell) or several clusters (e.g. the multiple dendrites of a neuron), but the mechanistic basis for unipolar or multipolar outcomes is unclear.
The design principles of Rho-GTPase circuits are captured by two-component reaction-diffusion models based on conserved aspects of Rho-GTPase biochemistry. We show that while multiple clusters tend to form initially, competition between clusters for cytoplasmic Rho-GTPase species resolve them to only one. Although the timescale of competition varies enormously depending on model parameters, a single factor explains a large majority of this variation. The dominant factor concerns the degree to which the maximal active GTPase concentration in a cluster approaches a “saturation point" determined by model parameters. We suggest that both saturation and the effect of saturation on competition timescale reflect fundamental properties of the Rho-GTPase polarity machinery, regardless of the specific feedback mechanism. To access whether this principle is translatable to biological systems, we further test this theory in the budding yeast, where competition between clusters guarantee unipolarity in wildtype, but in cytokinesis defect mutants, prolonged competition can lead to multiple simultaneously growing fronts.

Disclosure of Interest: None Declared

Controlling cell fate specification system based on network structure

Kenji Kobayashi[1], Kazuki Maeda[2], Miki Tokuoka[1], Yutaka Satou[1], Atsushi Mochizuki[* 3]
[1]Graduate School of Science, Kyoto University, Kyoto, [2]School of Science and Technology, Kwansei Gakuin University, Sanda, Hyogo, [3]Institute for Frontier Life and Medical Sciences, Kyoto University, Kyoto, Japan

Secondary topic : Developmental Systems Biology

Your abstract : By the success of modern biology we have many examples of large networks which describe regulatory interactions between a large number of genes. On the other hand, we have a limited understanding for the dynamics of molecular activity based on such complex networks. To overcome these problems, we developed *Linkage Logic theory* to analyze the dynamics of complex systems based on information of the regulatory linkages alone. It assures that i) any long-term dynamical behavior of the whole system can be identified/controlled by a subset of molecules in the network, and that ii) the subset is determined from the regulatory linkage alone as a feedback vertex set (FVS) of the network. We applied this theory to the gene regulatory network for cell differentiation of ascidian embryo, which includes more than 90 genes. From the analysis, dynamical attractors possibly generated by the network should be identified/controlled by only 5 genes, if the information of the network structure is correct. We verified our prediction by combinatorial experiments of knockdown and overexpression by using ascidian embryos. We found that almost all of the expected cell types, six among seven major tissues, could be induced by experimental manipulations of these five genes.

1. Kobayashi., *et al. iScience* (2018) doi:10.1016/j.isci.2018.05.004

Disclosure of Interest: None Declared

Systems Medicine B
WEDNESDAY, OCTOBER 31 – 10:00 AM – 12:30 PM

Characterization of different sepsis phases by virtual infection modeling of the innate immune response in human whole blood

Teresa Lehnert[*1,2], Ines Leonhardt[2,3], Kerstin Hünniger[3,4], Oliver Kurzai[2,3,4], Marc Thilo Figge[1,2,5]
[1]Applied Systems Biology, Leibniz Institute for Natural Product Research and Infection Biology, Hans Knöll Institute (HKI), [2]Center for Sepsis Control and Care (CSCC), University Hospital Jena, [3]Fungal Septomics, Leibniz Institute for Natural Product Research and Infection Biology, Hans Knöll Institute (HKI), Jena, [4]Medical Microbiology and Mycology, Institute for Hygiene and Microbiology, Würzburg, [5]Faculty of Biological Sciences, Friedrich Schiller University , Jena, Germany

Secondary topic : Multiscale Systems Biology

Your abstract : Sepsis is a major cause of death and morbidity worldwide and known as a heterogeneous clinical syndrome described by marked inhomogeneous changes of the immune state in terms of diverse pathological conditions and variable disease kinetics in individual patients. Therefore, it is of major importance to develop tools that enable stratification of septic patients and predict the efficacies of tailor-made therapeutic interventions. In this study, we apply mathematical modeling combined with human whole-blood infection assays to quantify the immune response to infections in donors with distinct immune states.

We developed a state-based virtual infection model (1,2) representing essential innate immune mechanisms during whole-blood infection. In order to quantify the *a priori* unknown rates of immune mechanisms, the model was calibrated to whole-blood infection assays using the parameter estimation algorithm *simulated annealing*. First, we quantified the immune response in blood samples of healthy donors that were infected with either the bacterial pathogen *Staphylococcus aureus* or the fungal pathogen *Candida albicans*. Thereby, we identified clear differences in the immune response to these pathogens, *i.e.* in the parameter values of immune cell reaction rates. Building on this work, we are currently applying the state-based model to quantify the immune response to different pathogens in blood samples of patients who underwent cardiac surgery with extracorporeal circulation. This surgery provides an inflammatory stimulus that is both time-defined and relatively homogeneous. With the ability to investigate the blood of the same patient at defined time points before and after surgery, inter-individual differences and the effects of inflammation could be clearly distinguished. The analysis of several patients revealed an increase in white blood cell count after surgery as well as variations in immune cell reaction rates. Additionally, we found that pathogen-specific patterns of the immune responses before surgery diminish after the surgery.

In order to bring this study closer to the clinical situation, in the future we plant to quantify blood samples from sepsis patients. This will allow identifying patterns of the dysregulated immune homeostasis providing functional classifiers for the differentiation and categorization of sepsis patients.

(1) Hüniger and Lehnert *et al.* (2014) PLOS Comp. Biol. 10(2), e1003479
(2) Lehnert and Timme *et al.* (2015) Front. Microbiol. 6(608)

Disclosure of Interest: None Declared

Automated image analysis of mast cell - dendritic cell interactions reveals weapon transfer in immune system

Anna Medyukhina[* 1], Jan Dudeck[2], Anne Dudeck[2], Marc Thilo Figge[1, 3]
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Your abstract : Dendritic cells (DCs) are innate immune cells that patrol the tissue for pathogens. They take up antigens and migrate to the lymph nodes where they present antigen-loaded MHCII (major histocompatibility complex class II) proteins to T cells, which then proliferate and home back to the tissue to induce inflammation. The re-activation of T cells in the inflamed peripheral tissue, however, is not well understood.

Longitudinal intravital two-photon microscopy of murine ear skin revealed another important player in this process [1]: DCs intensely interact with mast cells (MCs) prior to leaving the tissue and transfer to them part of their proteins. To prove that these interactions play a central role in the inflammatory response, rather than occurring by chance, we analyzed hundreds of images and videos from different time points during the course of inflammation. To objectively quantify these image data, we developed an automated image analysis pipeline, which extracts individual cells and detects and quantifies MC-DC interactions. This requires to distinguish between cell contacts and autofluorescence artifacts from hairs and corneocytes and was realized by taking into account not only the intensities of the corresponding fluorescent channels, but also the size and shape of the detected objects, as well as the collagen content visualized by the second harmonic generation modality.

The developed software enabled to reliably identify MC-DC contacts and quantify their number, duration, and dynamics. We found that during early stages of inflammation, DCs dynamically scan MCs, whereas at a later stage, long-lasting synapse-like contacts predominate, which culminate in protein transfer from DC to MC. The transferred protein pool turned out to include antigen-loaded MHCII, which – as subsequently confirmed by further ex-vivo experiments – armed the MCs with the ability to activate T cells. Such DC-to-MC weapon transfer suggests that MCs may activate the arrived T cells at the spot of inflammation when DCs are absent.

[1] Dudeck J*, Medyukhina A*, Froebel J, Svensson C-M, Kotrba J, Gerlach M, Gradtke A-C, Schröder B, Speier S, Figge MT**, Dudeck A**; *authors contributed equally; **corresponding authors, authors contributed equally (2017) Mast cells acquire MHCII from dendritic cells during skin inflammation. *The Journal of Experimental Medicine* 214(12), 3791-3811.

Disclosure of Interest: None Declared

Non-linear mixed effects models to study inter-individual variability in CD8 T cell immune responses in mice.

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Secondary topic : Methodological developments for Systems Biology

Your abstract : Following an infection by an intracellular pathogen, the immune system triggers different mechanisms that lead to the activation and expansion of killer CD8 T cells that will eliminate the pathogen. In the present work, we analyze the CD8 T cell immune response to an antigen that cells never encountered before (primary response). For this, we rely on quantitative experimental data corresponding to antigen specific CD8 T cell counts measured at different times on groups of infected mice. CD8 T cell counts display a significant inter-individual mice-to-mice variability. We propose to study the observed inter-individual variability with non-linear mixed effects models.

A mathematical model based on ordinary differential equations has been proposed to describe an average behavior of CD8 T cells in response to a pathogen in mice [1]. To study inter-individual heterogeneity we aim at estimating the variability of the model parameters within the population of mice. To do so, the individual parameters are assumed to be drawn from a probabilistic distribution characterized by a mean and a standard deviation. Once the mean and standard deviation of each parameter are estimated, parameters of each individual are estimated. This method enables access to the average behavior as well as individual ones. Estimations were performed with stochastic approximation expectation-maximization algorithm implemented in the Monolix software [2].

We first generated synthetic data in order to understand how variability in CD8 T cell counts might emerge from variability in the parameters. Then, we estimated the parameters from the experimental data, for two different responses to the same antigen: one where the antigen is carried by a pathogen, and one where it is carried by cancer cells. Altogether, this study enables us to identify the parameters that vary the most within the population, and to compare parameter mean and variance between those two conditions. We propose a minimal model that explains the heterogeneity in CD8 T cells immune responses on synthetic data as well as on measured cell counts. Finally, the consequences for vaccine development will be discussed.

[1] F. Crauste et al. (2017) Identication of Nascent Memory CD8 T Cells and Modeling of Their Ontogeny, Cell Systems. 4, 306-317.
[2] B. Delyon, M. Lavielle and E. Moulines. (1999) Convergence of a stochastic approximation version of the EM algorithm, Ann. Statist. 27, 94-128.

Disclosure of Interest: None Declared

Modelling bistable tumour population dynamics to design effective treatment strategies

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Secondary topic : Modelling Networks and Circuits

Your abstract : Despite recent advances in targeted drugs and immunotherapy, cancer remains “the king of all maladies” due to inevitable emergence of resistance. Drug resistance is thought to be driven by mutations, as well as other events such as dynamic tumour plasticity that deregulate pathway activities and regulatory programs of a highly heterogeneous population of tumour cells. In this study, we propose a modelling framework to simulate population dynamics of tumour cells with distinct intrinsic cell states during treatment with varying drug doses. Cell states are determined by coordinated activities and patterns of aberrant activation/deregulation of multiple interconnected oncogenic pathways, their downstream effectors and feedback loops, including those involving the tumour and immune microenvironments. In order to significantly affect the viability and stability of oncogenic states it is necessary to elucidate strategies based on effective treatments with targeted agents that target these pathways. Under this framework, we built a simple model to capture drug resistance characteristics of BRAF-mutant melanoma, where two cell states are described by two mutually inhibitory – main and alternative – pathways. Cells with an activated main pathway are proliferative yet sensitive to the BRAF inhibitor, and cells with an activated alternative pathway are quiescent but resistant to the drug. We describe a dynamical process of tumour growth under various drug regimens using the explicit solution of mean-field equations. Based on these solutions, we compare efficacy of three main treatment strategies: static treatments with continuous and constant dosages, periodic treatments with regular intermittent phases and drug holidays, and treatments based on optimal control theory (OCT). Based on these analysis, periodic treatments outperformed static treatments with a considerable margin, while treatments based on OCT outperformed the best periodic treatment. Our results provide theoretical insights regarding optimal cancer treatment modalities for tumours with heterogeneous populations of cancer cells, and may guide the development of optimal therapeutic strategies to circumvent drug resistance and due to tumour plasticity.

Disclosure of Interest: None Declared

The complex life of Smad isoforms determines gene expression in hepatocellular carcinoma

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Secondary topic : Modelling Networks and Circuits

Your abstract : Transforming growth factor β (TGFβ) leads to the phosphorylation of the Smad isoforms Smad2 and Smad3. Doubly phosphorylated Smad proteins (ppSmad2 and ppSmad3) together with Smad4 can form different trimeric Smad complexes. The Smad complexes in turn activate a broad spectrum of target genes. It remains unresolved which of the possible Smad complexes are formed in cellular contexts and how these contribute to gene expression. We combine time- and dose-resolved experimental data obtained by quantitative immunoblotting and site-specific mass spectrometry with a computational selection strategy by L_1 regularization. Our approach enabled us to predict and provide experimental evidence for the three most relevant Smad complexes in the mouse hepatoma cell line Hepa1-6: ppSmad2:ppSmad3:ppSmad3, ppSmad2:Smad4:Smad4, and ppSmad2:ppSmad3:Smad4. Utilizing dynamic pathway modeling, we specify the contribution of each of these Smad complexes to the expression of representative Smad target genes, and show that these contributions are conserved in human hepatoma cell lines and primary hepatocytes. We predict based on gene expression data of patient samples increased amounts of Smad2/3/4 proteins and Smad2 phosphorylation as hallmarks of hepatocellular carcinoma and experimentally verify this prediction. Our findings demonstrate that modeling approaches can disentangle the complexity of transcription factor complex formation and its impact on gene expression. *Lucarelli et al. 2018, Resolving the Combinatorial Complexity of Smad Protein Complex Formation and Its Link to Gene Expression. Cell Systems 6(1):75-89.e11.*

Disclosure of Interest: None Declared

Systems Medicine C
WEDNESDAY, OCTOBER 31 – 04:00 PM – 05:40 PM

Machine learning pipeline for pathways analysis with reverse phase microarray data of non-small cell lung cancer cell lines and different drugs

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Your abstract : About 80% of lung cancer diagnoses are Non-small cell lung cancer (NSCLC), the most common subtype of lung cancer. Since NSCLCs are insensitive to standard chemotherapy, the development of personalized therapies is a key issue in oncological research. The purpose of this work was to apply a cancer systems biology pipeline to unravel the response of tumor cells to target treatments and to investigate mechanisms of resistance by analyzing different pathways in NSCLC. We used a machine learning tool to study the role of KRAS, one of the most widespread oncogenic mutations. Reverse phase protein microarray (RPPA) was employed to quantify the activation level of 183 proteins in 8 NSCLC cell lines (CLs), 5 KRAS mutant (MUT) and 3 KRAS wild-type (WT). Each CL was treated with Selumetinib (SE) in combination with Everolimus (EV) or Tamoxifen (TA). Proteins were also measured on the baseline and on CLs with only Dimethyl Sulfoxide. The resulting dataset comprises time series of 6 time points: 5 minutes, 1, 2, 6 and 24 hours. In order to identify the subset of proteins that optimally distinguishes KRAS MUT and WT samples, we utilized Recursive Feature Elimination with Support Vector Machine (RFE-SVM). Finally, we mapped the obtained relevant proteins to protein interaction networks, through Reactome FI, a Cytoscape plugin. RFE-SVM was applied to both WT and MUT CLs to study the effect of the two treatments. As regards WT CLs, apart from a transient activation of different pathways, in the long period only the MAPK pathway is altered when CLs are given the SE and EV or the SE and TA. On the other hand, MUT CLs showed that numerous signaling pathways were active in different time intervals. For instance, the combination of SE with EV activated NGFR, PDGFR, PI3K-Akt and Interleukins pathways in the first hour of treatment. Instead, the combination of SE with TA altered EGFR, mTOR and PI3K-Akt pathways after 24 hours from the treatment. Due to the high complexity of interaction networks of MUT samples, we performed unsupervised cluster analysis among proteins with the purpose of dividing networks into different biological modules. In conclusion, we proposed a new computational framework combining *omics* data and a machine learning algorithms, applied to a proteomic dataset of NSCLC CLs. This approach disclosed that MUT and WT CLs had a completely different response to the two combination of drugs and that in MUT CLs the two treatments caused a different response rate.

Disclosure of Interest: None Declared

Putting the squeeze on RNA-seq data: mapping individualized genetic and epigenetic regulation in complex diseases

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Secondary topic : Multi-omics

Your abstract : The allele specific resolution of RNA sequencing technology enables estimation of allelic imbalance, a state where the two alleles of a gene are expressed at a ratio differing from the expected 1:1. A key underlying mechanism for allelic imbalance, also commonly referred to as allele specific expression, is the presence of truncating variants leading to nonsense-mediated decay of one of the two alleles. Additionally, genetic regulation of transcription and splicing, as well as epigenetic modifications through imprinting and interactions with the environment, contribute to an observed imbalance. Most importantly though, allelic imbalance can be reliably analyzed at the level of the individual subject.

Within the Maastricht Center for Systems Biology we have recently developed an approach that maps out which genes lose part of their functionality through the process of allelic imbalance. Our method combines rigorous quality control, robust statistical analysis and a novel network based approach. In a pilot study within a local cardiometabolic cohort, we see that the strength of the imbalance shows striking heterogeneity between subjects that would be lost using traditional group based approaches. Our novel network approach is able to reveal clusters of genes that are co-imbalanced across subjects, as well as clusters of subjects sharing co-imbalanced genes. Strikingly, this co-imbalance is associated with both the severity and nature of cardiometabolic traits, postulating a shift towards disease contributing alleles during disease progression by interplay between genetic and epigenetic mechanisms. We are able to determine the contribution of the former by using RNA sequencing derived genotyping and splicing data, while the latter can subsequently be estimated based on residual variation.

Taken together, allelic imbalance analysis complements established approaches that detect the presence of genetic variants, or differential expression or splicing across groups, by enabling analysis on the level of the individual subject. Moreover, allelic imbalance analysis enables elucidating the interaction between genetic and epigenetic regulation in complex traits using a single, established and affordable technology and hence could be a boon for clinical applications.

Disclosure of Interest: None Declared

Therapeutic understanding of human dopaminergic system in neurological diseases - a systems biology approach

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Secondary topic : Systems Neurosciences

Your abstract : Dopamine, a key neurotransmitter that conducts both inhibitory and excitatory synaptic transmission, functions by binding to specific G-protein coupled receptors– Dopamine Receptors (DRs). Modulation of functional activity of these receptors has been well-established in the complex neurological diseases such as Schizophrenia, Parkinson's and Bipolar disorder. Till date, most of the research efforts have principally targeted DR family to identify therapeutic candidates for such diseases. Complex diseases indeed entail an intricate interplay of multiple physiological pathways and processes and hence cannot be understood by examining a single protein or pathway. In view of this, we employed a holistic approach to capture comprehensive interactions of various candidate proteins associated with human DRs through Protein-Protein Interaction Network analysis and we termed it as DRIN (Dopamine Receptors Interaction Network). We investigated its topology and function, and also studied the potentiality of DRIN in overlapping neurological disorders using statistical and computational approaches. Remarkably, a major portion of DRIN showed high enrichment of established Schizophrenia Disease Genes (SDG). Amongst different tissues isolated from various regions of human brain, we inspected co-expression network of SDG, examined their fundamental network topologies and determined a common sub-network to effectively pinpoint crucial disease genes. The findings piloted the design of potential CNS permeable compounds using Computer Aided Drug Design (CADD) approaches to target the identified novel therapeutic candidates for Schizophrenia. Furthermore, Dopamine Receptor D2 (DRD2) surfaced as important target in DRIN. We predicted 3D structure of DRD2 protein and refined using Molecular Dynamics (MD) simulations. The third Intracellular Loop (ICL3) of DRD2 demonstrated strong genetic association to several complex diseases. We investigated deleterious effect of a key serine to cysteine mutation (S311C) in ICL3 of DRD2 on ligand binding and downstream signaling using protein-ligand and protein-protein docking followed by atomistic MD simulations. Our study presents a profoundly integrated framework encompassing network theory, molecular modeling and CADD to establish a valuable therapy to understand neurological disorders.

Disclosure of Interest: None Declared

Transforming physiological models from mice to humans - the case of iron homeostasis.

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Secondary topic : Methodological developments for Systems Biology

Your abstract : Much biomedical research is carried out with model animals, such as the mouse, but with the the target to apply it to humans. Thus there is an inherent need to be able to translate results obtained from model animals to the corresponding human context. This problem is general and spans both experimental as well as computational research. Focused on the specific problem of modeling iron physiology in mammals, we developed a workflow that has allowed us to first construct a mouse model and then translate it to a human equivalent. Both models were validated with data specific for their own species. We will describe the methodology used, the data sources, and the obstacles encountered. The two major challenges are for the model to be able to cover the wide range of variability seen in human subjects, and which sources of data can be practically used for calibration of the master model to specific individuals. Many of these challenges are not limited to iron metabolism but are rather of a more general nature. It has become evident to us that it would have been extremely difficult to generate the human model without the aid of the mouse model, and we expect this to be similar in other physiological domains.

Iron is indispensable for life, however, unliganded iron is toxic and has been implicated in the pathogenesis of many diseases and aging. Disruptions of iron regulation result in several widely prevalent diseases, such as anemias and hemochromatosis. Our computational models represent iron regulation at the whole-body level including absorption, distribution, and metabolism. The models are calibrated by estimating parameters using ferrokinetic data, then they are validated against data from mutations that lead to hemochromatosis, β-thalassemia, atransferrinemia and anemia of inflammation. From this approach of calibration and validation, we have identified a minimal set of regulatory mechanisms needed to properly explain iron distribution in the body. The utility of this model for a (personalized) systems medicine approach is illustrated with its application to simulate disease interventions.

Disclosure of Interest: None Declared

A circadian metabolomics atlas of the body under chronic nutrient stress

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Secondary topic : Quantitative Systems Physiology
Your abstract :
Metabolic diseases are often characterized by circadian misalignment within and across different tissues. Yet how altered coordination and communication among tissue clocks is related to specific pathogenic mechanisms remains largely unknown. To gain novel perspectives on these relationships we applied an integrated systems biology approach.
Performing circadian metabolomics profiling on several different tissues simultaneously, we present a comprehensive temporal and spatial atlas of in vivo circadian metabolism in the context of systemic energy balance, and under chronic nutrient stress (high fat diet, HFD). Comparative analysis reveals how the repertoires of tissue circadian metabolism are linked and gated to specific temporal windows under conditions of energy balance. In addition, we have identified and reconstructed a vast array of common and tissue-specific metabolite alterations elicited by HFD. Our study reveals highly specialized communication and coherence among tissue clocks, and their rewiring in the context of nutrient challenge. Overall, we illustrate how dynamic metabolic relationships can be reconstructed over time, and how integration of circadian metabolomics data from multiple tissues can improve our understanding of health and disease.

Disclosure of Interest: None Declared