monoribosomes. These ribosome-protected mRNA fragments are purified and prepared for high throughput sequencing to map the position of cellular ribosomes and quantify levels of translation. By comparing ribosome profiling levels with RNA-seq measurements of mRNA levels we find many new cases of genes whose translation only occurs during the proper phase of the cell cycle. We find that a majority of ORFs have a >2-fold change in translation efficiency during the cell cycle. This suggests that *Caulobacter* uses cell cycle-specific regulation of translation to ensure proper timing of gene expression.

Computational Systems Biology

1895-Pos Board B625

Modelling the Mechanics of the Circulation: Blood Rheology and Atherosclerosis

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In this work, we test the hypothesis that a redistribution of blood particles is related to predilection sites of atherosclerosis,which is characterised by the deposition of lipid material and inflammatory cells. The focal distribution of lesions, shear stress,and mass transport play an important role[1] because shear stress scales inversely with enhanced transport of species in the vessel wall. Also, because 46% of blood volume is made up of particles, blood compounds have wide-reaching effects on the coupling of blood flow to the vessel walls. Indeed, some works have shown changes in flow rate, apparent viscosity and flow patterns due to particle's shape and/or concentration[2,3,4,5,6] besides literature usually focus on microcirculation that is driven by diffusive transport and differs in many other ways to the mechanics of circulation in large vessels. Here, we present some results(Fig.1) to support the hypothesis that flow trends related to atheroma development might be more accurately described by multiphase flow models[7], which is the subject of ongoing research.

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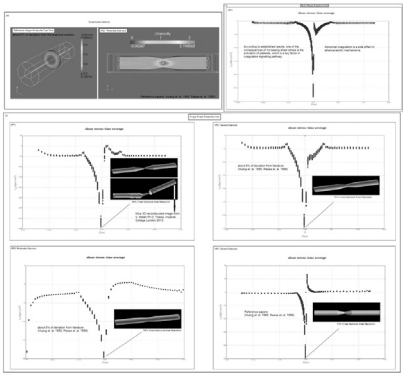

Fig. 1 Blood Flow Phenomena $Re = 100$: (a) Streamwise velocity in a Poiseuille pipe flow compared to a model of moderate lumen narrowing; (b) Poiseuille single phase – patterns of shear stress considering four levels of lumen narrowing in atheroma development; (c) Pulsatile multi phase: the shear stress for a model of severe lumen narrowing increases compared to Poiseuille single phase results.

1896-Pos Board B626

Stochastic Discrete Effects in a Simple Gene Circuit with Delayed Negative Feedback

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Negative feedback loops are ubiquitous motifs in gene regulation processes, providing cells with control mechanisms to perform key decisions. Consequently, they have received a lot of recent attention in the efficient design of synthetic gene circuits. The interconnected biochemical reactions composing negative feedback loops are discrete and random by nature, and are more accurately described by stochastic models. These models, however, often make assumptions yielding erroneous predictions, or simply miss out on important discrete stochastic effects. One such common omission is the explicit delays that separate the initiation of transcription and translation from the appearance of their corresponding functional products. Thus, delay-induced stochastic oscillations and other delay-induced stochastic discrete effects have remained relatively unexplored at the single-cell level. In our work (Zavala and Marquez-Lago, submitted), we study oscillatory and multimodal behavior in a simple gene circuit with delayed negative feedback by systematically analyzing the influence of negative feedback strength and transcriptional/translational delays on expression dynamics. We carry out single-cell simulations producing exact trajectories of the Delay Chemical Master Equation, thus avoiding any approximation errors, and demonstrate an oscillatory regime emerges through a stochastic Hopf bifurcation. Furthermore, we characterize conditions under which stochastic oscillations produce bursts, and vice versa. In conformity with previous results (Marquez-Lago et al., BiophysJ 2010) we show that the same gene circuit architecture is capable of multimodal behavior and burst-like expression. Most importantly, we describe how explicit delays produce novel non-classic effects, not yet reported in the literature.

1897-Pos Board B627

Predicting and Retrodicting Fate Patterns in C. elegans Vulval Development using Logic Programming

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Vulval development in *C. elegans* is a paradigm for understanding how cell fate determination leads to organogenesis. The fate pattern of a row of six cells is specified by spatial and temporal controls, and the competition of the LET-23/SEM-5/LET-60/MAPK and Delta/Notch signalling pathways. Formal verification techniques applied to state models of vulval development have been shown as a powerful approach for demonstrating how the signalling systems interact and determine cell fate. However, the computational requirements of verification approaches become prohibitive as model complexity increases. Here we apply a logic programming based approached to derive minimal models of vulval development, increasing the speed of prediction of fate pattern from genotype by up to four orders of magnitude. This increase in speed further allows us to infer or 'retrodict' genotypes from the final fate pattern. We apply this new technique to understand how highly variable cell fates arises when the precise morphogen gradient of LIN-3 is effectively randomised by diffusion in *dig-1* mutations. We further apply this to the study of *let-23* mosaic mutations, and find that the resulting model refinements reconcile our approach with historical experimental data. Based our new findings we propose that logic programming provides an efficient approach for design and analysis of experimental data.

1898-Pos Board B628

Modeling Electrical Activity in Intestinal L-Cells

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Glucagon-like peptide 1 (GLP1) is an insulinotropic hormone released from intestinal L-cells in response to food ingestion. It is responsible for the so-called incretin effect, i.e. the fact that glucose ingested orally elicits a greater insulin response than glucose administered intravenously, even when glucose concentrations in plasma are matched.

In addition, GLP1 inhibits glucagon secretion, slows gastric emptying, regulates appetite and food intake. All these actions have made GLP1 an appealing target for the development of new treatments of type 2 diabetes. In this context, the comprehension of the sensory and secretory pathways, which is still poorly understood, becomes essential. The stimulus-secretion pathway in L-cells includes electrical activity to transduce glucose sensing to calcium-stimulated exocytosis.

We build a mathematical Hodgkin-Huxley-like model of electrical activity of L-cells based on recent data on primary colonic L-cells. The model includes ATP-sensitive K+-channels (K(ATP)-channels), voltage gated Na^+- and K+-channels and low- and high-voltage activated Ca^{2+}-channels. The model incorporates also the sodium glucose cotransporter SGLT1, which has been reported to be the primary glucose sensing machinery in L-cells.

The model reproduces satisfactorily electrical activity consisting of action potentials in response to glucose. A role for sodium and calcium channels for the upstroke, and activation of potassium channels for the downstroke, is demonstrated by simulating ion channel blockage. Electrical activity is a result of the inward current due to sodium-glucose cotransport, proving the central role of SGLT1. K(ATP)-channel closure is shown to contribute to electrical activity, since lower K(ATP)-conductance reduces the threshold for SGLT1 conductance where electrical activity is initiated.

The model is shown to be useful for hypothesis testing and as a starting-point for future investigations of the signals underlying GLP-1 secretion, which might eventually lead to new antidiabetic drugs aiming at increasing endogenous GLP-1 release.

1899-Pos Board B629

Investigation of Novel Zap-70 Functionality in T Cell Signaling Pathways using Computational Modeling

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Aberrant regulation of cellular processes in immune systems can result in human disease. Therefore, we need a better understanding of the mechanistic

principles of biochemical signaling pathways that regulate immune responses. This study investigates a novel functionality of the tyrosine kinase zeta-associated protein Zap-70 in T cell signaling pathways, using the quantitative phosphoproteomics data obtained from our experimental collaborators. The Zap-70 alterations in cellular signaling pathways (loss of its function or expression) can cause an unusual form of severe combined immune deficiency (SCID) that often leads to fatal outcomes. Therefore, the analysis of signaling events using computational modeling and modern proteomics technique (e.g., stable isotopic labeling of amino acids in cell culture (SILAC)) provides a network map of possible molecular targets guiding disease diagnosis. Additionally, this network map presents information about the placement of newly observed phosphorylation sites in T cell signaling pathways across a time course after receptor stimulation. In this study, we tested several computational models of Zap-70 T cell signaling pathways to experiment with different hypotheses. Specifically, we calculated the phosphorylation levels of tyrosine residues of N- and C- terminals of immunoreceptor tyrosine-based activation motif (ITAM) for different expression levels of Zap-70 in T cells. We performed fully stochastic signaling simulations using stochastic simulation complier (SSC) developed in our lab and modeling of ordinary differential equations. Subsequently, the sensitivity analysis of deterministic simulations was performed for identifications of key proteins and biochemical reactions in signaling networks that regulate stochastic transitions leading to pathological cellular function. The calculated ITAM phosphorylation levels are well correlated with the corresponding experimental ones. Finally, using our computational modeling, we formulated novel testable hypotheses that can guide future experiments.

1900-Pos Board B630
Accelerating Systems Biology Computation: Rapid Estimation of Equilibrium and Kinetic Quantities via Weighted Ensemble Sampling
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We apply the ''weighted ensemble'' (WE) simulation strategy, previously employed in the context of molecular dynamics simulations, to a number of stochastic systems-biology models. WE is relatively easy to implement, does not require extensive hand-tuning of parameters, does not depend on the details of the simulation algorithm, and can facilitate the simulation of extremely rare events. We examine spatially homogeneous (stochastic chemical kinetics) models that range in complexity from a one-dimensional system to a system with 354 species and 3680 reactions, and also examine spatially resolved 3-D systems (simulated in MCell) containing ~10^3 to 10^6 molecules.
For the stochastic chemical kinetics systems, WE is able to produce accurate and efficient approximations of the joint probability distribution for all chemical species for all time t. WE is also able to efficiently extract mean first passage times for the systems, via the construction of a steady-state condition with feedback. WE exhibits speedups over ''brute-force'' in sampling rare events via the Gillespie direct Stochastic Simulation Algorithm ranging from ~10^12 to ~10^18 for characterizing rare states, and from ~10^2 to ~10^4 for finding mean first passage times.
WE is also used to study rare binding events in spatially resolved 3-D systems simulated with MCell. In a toy model, WE exhibits speed-ups on the order of 10^60 for the characterization of rare binding. We also present our ongoing efforts to apply the WE methodology to a spatial model of a frog neuromuscular junction.

1901-Pos Board B631
Negative Feedback and Crosstalk in the TGF-β Signaling Pathway
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The transforming growth factor-β (TGF-β) signaling pathway transduce extracellular signals into transcrip- tional responses controlling key cellular processes, such as differentiation, proliferation, and apoptosis, through a network of receptors. Defects along of the pathway have been associated with a wide range of diseases, including developmental diseases and a variety of cancer types. Here, we examine the role of the negative feedback through protein products of transcriptional regulation by mediator SMAD proteins in the behavior of the network by analyzing a novel, detailed computational model of the pathway. The model includes macromolecular assembly, receptor trafficking and signaling, activation of two SMAD channels, nucleocytoplasmic shuttling of smad-complexes, and feed-back through inhibitory SMADs. This computational model is able to accurately reproduce and explain experimental data in diverse cell types and our analysis uncovered the importance of negative-feedback-mediated crosstalking between channels in the TGF-β pathway. In addition, we identified key crosstalk points among pathways through literature mining approaches, by constructing a detailed ligand-receptor network for all the members of the TGF-β superfamily and mapping the interactions with other pathways.

1902-Pos Board B632
Spatio-Temporal Regulation of Mitotic Spindle Checkpoints
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Stable microtubule spindle attachments at the kinetochores (KT) - the microtubule binding platform on the chromosome - ensure faithful chromosome segregation in mitosis. Unstable KT-spindle attachment locally activates the spindle assembly checkpoint (SAC) - an inhibitory signal that halts mitotic progression of the entire cell. Only after the last KT gets properly attached, can SAC get silenced and chromosome segregation ensue. However, given the everlasting stochastic fluctuations and large chromosome number in the cell, the mechanism ensuring the robustness in the SAC silencing timing remains elusive. From the stably attached KT, key mitotic players, including SAC, stream toward the associated spindle pole. Incorporating such spatial-temporal regulation, we established a theoretical model that unprecedentedly accounted for the fidelity of SAC silencing. It revealed that spindle poles integrate the poleward streaming from the attached KTs. The unattached KTs divert the poleward streaming, competing with the spindle poles. The diversion disappears upon the last KT-spindle attachment, causing a larger jump in the spindle pole accumulation than all the previous KT-spindle attachments combined. This large jump robustly triggers SAC silencing from the spindle poles after and only after the last KT-spindle attachment. This mechanistic insight accounts for many intriguing observations on mitosis, including the biphasic taxol dosage-dependence of anaphase delay, the distinct SAC silencing patterns in merged cells with two spindles, the size scaling between the mitotic spindle and the cell, and the error-proneness of mammalian oocyte meiosis. We thus established a unified conceptual framework across species - the spatial-temporal regulation ensures the fidelity of SAC silencing.

1903-Pos Board B633
The Role of Cooperativity in Cell Signaling
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Sensory cells use surface receptors to detect environmental stimuli and initiate down stream signaling. Cooperative binding of ligands and ions is known to play a crucial role in enhancing the sensitivity of biochemical processes such as oxygen sensing by hemoglobin, but whether cooperativity enhances the fidelity with which a system can accurately detect a signal in a noisy background is poorly understood. Here, we explore the signal to noise ratio for several classes of cooperative signaling. We show that the signal to noise ratio depends on the number, connectivity, and underlying dynamics of the signaling network.

1904-Pos Board B634
Sensitivity Analysis and Model Reduction Applied to Adapting Biological Systems
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A common problem in systems biology is relating the relevant parameters of a mathematical model to its observed qualitative features. In this work, we study a nonlinear dynamic model of a biochemical system with an underlying network topology. The system is parameterized by a high-dimensional vector and it outputs multiple boolean functionalities. The first part of this work develops a regularized sensitivity analysis to determine parameter/functionality relationships and discusses the conditions under which these relationships may be generalized across parameter vectors and network topologies. The second part of this work discusses a method of reducing a given parameter/functionality relationship on a dense network topology to a similar relationship on a sparser network. Throughout this work, we apply our techniques to an established model of biochemical adaptation.

1905-Pos Board B635
Macromolecular Crowding Effects on Gene Regulation
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Studies of macromolecular crowding have shown its important effects on molecular transport and interactions in living cells. Less clear is the effect of crowding when its influence is incorporated into a complex network of interactions. Here we explore the effects of crowding on a model of gene transcription as a network of reactions involving transcription factors, RNA polymerases, and DNA binding sites for these proteins. The novelty of our approach is that we determine the effects of crowding on the rates of these reactions using