Saccharomyces cerevisiae, glucose is the preferred sugar that is metabolized and is also a stimulus that controls the expression level of some quarter of the yeast's genes. Interestingly, yeast can measure the level of extracellular glucose through its various sensors, but not directly how much glucose it's importing. Two of these sensors, Snf3 and Rgt2, detect the concentration of extracellular glucose and accordingly regulate the transcription of the passive hexose transporters (HXTs) that are essential for glucose uptake in yeast. Here, we show that when the transcription of HXTs is controlled independently of the two sensors, surprising behaviors in the cell's growth rate are observed. In particular, both increase in glucose uptake rate (GUR) and the extracellular glucose concentration can each lead to substantial decrease in cell's growth rate. We therefore show that the growth rate of the cell in batch cultures is not just a function of how much glucose the cell eats, but also depends on how much glucose the cell senses outside. We attribute these growth rate behaviors to an imbalance between availability and consumption of glucose. By studying a *snf3Δ*, *rgt2Δ* mutant, the two sensors are shown to have an additional role in determining the growth rate than just through the transcriptional control of the HXTs. Furthermore, we have discovered that when just one of the main hexose transporters (HXT1~4, and HXT6) is present in a cell, glucose-sensitive post-transcriptional controls of that HXT other than the known endocytosis mechanism exist. Finally, we use an analytical model to reveal constraints placed on the synthesis of each HXTs to ensure proper scaling of GUR with extracellular glucose concentration.

1548-Pos Board B392

Modeling Intercellular MAPK Signaling in an Epithelial Wound Healing Assay

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Recent experiments in epithelial wound healing have demonstrated the necessity of MAPK activation for coordinated cell movement after damage. This MAPK activity is characterized by two wave-like phenomena. One MAPK ''rebounding wave'' that originates immediately after injury, propagates deep into the cell layer, and then regresses back to the wound interface. The second MAPK wave is a slow developing, sustained wave that propagates from the wound interface. Experimentalists have suggested that the first wave is originated by reactive oxygen species (ROS) generated at the time of injury. We develop a mechanistic diffusion-convection model that produces the observed behavior by taking advantage of the coupling between ligand (e.g. EGF) and ROS species in the activation of the MAPK cascade. In our model, the second wave is initiated, and sustained by the stresses induced by the slow cell movement toward the injury. We explore the bi-stability of the model in connection with the bi-stability of the MAPK cascade. In particular, we look for traveling wave solutions of the model and their properties under various regimes.

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Modeling cAMP-cGMP Crosstalk in the Cardiac Myocyte

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While the role of nitric oxide (NO) in regulating cardiac function through vascular smooth muscle relaxation has been characterized over the past 15 years, NO's effects in the cardiac myocyte have yet to be resolved. The addition of NO to these cells has been reported to cause a biphasic response; NO either increases or decreases cardiac contractility depending on its concentration. Proposed mechanisms for this response include a number of factors, ranging from direct nitrosylation of the ryanodine receptor by NO to modulation of the beta-adrenergic signaling pathway by NO-induced cGMP. This latter interaction is supported by experimental data showing a concomitant biphasic response of the L-type calcium current.

In order to elucidate the mechanisms underlying the biphasic response of the L-type calcium current to NO, we have developed a model combining descriptions of cAMP production via the beta-adrenergic signaling pathway and cGMP production via a NO signaling pathway. The cAMP-cGMP crosstalk model couples the production of cGMP by guanylyl cyclase to the beta-adrenergic signaling pathway via cGMP-activated and cGMP-inhibited cAMP phosphodiesterases (PDEs.) Integrative regulation of cAMP concentration will ultimately regulate the L-type calcium current, via altered activation of protein kinase A.

We hypothesized that the opposing behavior of these two cGMP-regulated cAMP PDEs leads to the biphasic effects on L-type calcium current seen experimentally.

To test this hypothesis, a model was formulated from existing models describing cGMP synthesis and beta-adrenergic control of L-type calcium current. These two pathway models were coupled using enzyme kinetic data describing the PDEs. Simulations from the model combining these two pathways show that the interplay between these two cGMP-regulated cAMP PDEs gives rise to the biphasic response of the L-type calcium current. Supported by R33HL87345.

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Cdc14-release Oscillation is Separable from Cell-cycle Progression, and Modulated by Clb-Cdk

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A free-running Cyclin oscillator suggests that the oscillation of Cyclin dependent kinase(Cdk) activity can lead to periodicity of cell-cycle events. In budding yeast S. cerevisiae mitotic Cyclin activity is primarily antagonised by the phosphatase Cdc14 which is released from nucleolus in late mitosis and becomes active to promote exit from mitosis. We devised a quantitative assay to study the effect of B-Cyclin on Cdc14 localization. By introducing physiological concentration of nondegradable Clb2-kd into the cell, we found that Cdc14-localization status became oscillating and uncoupled from cell-cycle progression. The frequency of this oscillation is controlled by Clb2-kd concentration, and saturated at twice the frequency of a normal cell-cycle. This observation suggests that cell-cycle progression may be controlled synergistically by kinase and phosphatase oscillators. We proposed a model for the cell-cycle-independent Cdc14 oscillation being a negative feedback oscillator involving the activation of APC-Cdh1 by Cdc14 and the subsequent degradation of polo kinase.

1551-Pos Board B395

Modeling Extrinsic Apoptosis Regulatory Network Pathways Using A Rules-based Framework

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We describe a systems approach to combine mathematical modeling and experimental measurement in the study of apoptosis in mammalian cells. The apoptotic signal is an important all-or-nothing mechanism which must be tightly regulated in the cell. Our focus will be on the role of pro and anti-apoptotic proteins in the extrinsic apoptosis signaling pathway leading to the formation of pores at the mitochondrial membrane by BAK and BAX proteins. This network is a prototypical cue-signal-response-feedback pathway of high biomedical importance. Construction of mathematical signal transduction models that recapitulate key features of signaling pathways as they exist in cells is currently very difficult, in large part because few tools are available to assemble, validate and update large dynamical models. We aim to implement novel methodologies based on ''rules-based'' techniques to allow for a flexible treatment of this complex network model. The calibration of such a model and application to ongoing experimental work in our laboratory is an important aspect of this work. We report our ongoing work on this subject paying particular attention to the rules-based building framework, the calibration steps and the use of experimental data for model calibration and validation.

1552-Pos Board B396

A Graded Response of a Transcription Factor to Increasing Doses of External Stimuli: A Thermodynamic Framework Describing the Behavior of NF-kB

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A paradigm in transcriptional regulation is that a graded increase in transcription factor (TF) concentration is ''digitally'' translated into an on/off transcriptional response by means of cooperative TF binding to adjacent DNA binding sites. Such paradigm stems from the analysis of TFs operating in developmental processes, notably embryonic segmentation, that require the definition of sharp borders separating different body regions.

Here we show that NF-kB, a key TF responsible for the expression of genes implicated in the inflammatory and immune responses, is an ''analogical'' transcriptional regulator. We demonstrate that increasing doses of inflammatory stimuli lead to gradually increasing concentrations of NF-kB in the cell nucleus, which in turn are translated into gradually increasing levels of transcriptional activity of NF-kB target genes. Differently to what observed in developmental systems, we show that the number of NF-kB binding sites in