that control the behavior of the signal transduction networks. We focus specially on the role of the feedback through protein products of transcriptional regulation by SMADs in the behavior of the network. This computational model is able to reproduce, and explain counterintuitive experimental data. Our analysis allowed us to get key insights into the understanding of the dual opposing role of TGF-beta as tumor suppressor and tumor promoter in cancer and similar dual opposing roles of these signaling pathways observed in other diseases.

903-Pos Board B703
Mathematical Analysis of Bursting Mechanisms in Pancreatic β-Cells
Chae Young Cha, Yasuhiro Nakamura, Enrique Santos, Akinori Noma.

Based on extensive experimental studies, we developed a computer model of pancreatic beta cells, which is quiescent at low glucose concentration (G < 6.5 mM), and shows burst-interburst electrical events (7-16 mM) and continuous action potential burst at high G (> 18 mM). The lead-potential analysis applied to the interburst period indicated that the gradual activation of I_{Ca}, dependent Ca^{2+} current (I_{Ca,L}) is responsible for the spontaneous depolarization. The deactivation of ATP-sensitive K^{+} current (I_{KATP}) by the increase in ATP/ADP ratio during the interburst is also responsible at low G. On the other hand, at higher G the activation of I_{KATP} is nearly suppressed by the rapid ATP production. Instead, the accumulation of intracellular Na^{+} interrupted the burst and successive recovery from the Na^{+} load during the interburst period induced the intermittent burst through the outward Na^{+}/K^{+} pump current. In the bifurcation analysis, we separated the model variables into fast and slow ones to investigate the mechanisms underlying the mode changes between burst and interburst activity. We found equilibrium points (E_p), V_m of which correspond to zero-current potentials of the steady-state I-V curve. We demonstrate that multiple slow factors, such as [ATP], [MgADP], [Ca^{2+}] in the endoplasmic reticulum or ultra-slow inactivation of Ca^{2+} channels are involved in the mode changes of membrane excitability. In conclusion, the mathematical analysis, when applied to the physiological models, provided strong clue to clarify the fundamental mechanisms underlying the generation of burst activity.

904-Pos Board B704
Simulations Predict that Competing Gradients of VEGF and sFlt1 Alter VEGF Receptor Activation
Yasmin L. Hashambhoy, Joanna C. Chappell, Alex Nguyen, Shayan M. Peirce, Victoria L. Bautch, Feilim Mac Gabhann.

We have created an experimentally-based computational model describing spatial transport of vascular endothelial growth factor (VEGF) and its receptors to quantitatively understand how guidance cues may modulate blood vessel sprout growth. VEGF binds to endothelial cells and initiates angiogenesis. Both VEGF concentration and VEGF gradients may control sprout formation. Soluble VEGF receptor 1 (sFlt1) can bind and sequester VEGF. Based on observations in developing vasculature, we hypothesize that a local reduction in sFlt1 expression can increase locally available VEGF and thus control angiogenesis. However, the complex VEGF interaction network makes it difficult to isolate how individual proteins contribute to the spatial distribution of the growth factor using experiments alone. Our computational model represents the local environment of a single blood vessel and nearby tissue and directly incorporates the network of VEGF interactions. In the model, parenchymal cells secrete VEGF which diffuses through interstitial space and binds extracellular matrix (ECM) and sFlt1. VEGF binds endothelial cells via membrane-bound receptors Flt1 and Flk1, and endothelial cells secrete sFlt1. Additionally, the model accounts for degradation of VEGF and sFlt1 as well as internalization of receptor-bound ligands. Using partial differential equations, we simulate this system, which is constrained by experimentally-derived parameters. Our simulations show that when a sprout-leading tip cell secretes less sFlt1 than neighboring cells, there is decreased local sFlt1 sequestration of VEGF, thus resulting in augmented VEGF-Flk1 levels on the surface of the low-sFlt1 secreting tip cell. This could lead to sprout generation. We also show how variations in sFlt1 secretion and tip cell configuration may affect the gradients of guidance cues and directionality of sprout growth.

905-Pos Board B705
Understanding and Tracking Pro- and Anti-Apoptotic BCL-2 protein Interactions and their Relation to Cancer in Extrinsic Apoptosis
Carlos F. Lopez, Jeremy L. Muhlich, Peter K. Sorger.

We describe a systems approach to combine mathematical modeling and experimental measurement in the study of signal transduction in mammalian cells. Our focus is on the BCL-2 family of proteins and their interplay in extrinsic apoptosis. Construction of mathematical signal transduction models that recapitulate key features of signaling pathways as they exist in cells is currently very difficult. To circumvent this, we employ a novel rules-based modeling approach to manage and track high-level biological knowledge and translate this knowledge to mathematical models of extrinsic apoptosis. We present results that use experimental data as a foundation to explain
seemingly contradictory interactions among Bcl-2 proteins and their contributions to mitochondrial outer membrane permeabilization as inhibitors, promoters, or sensitizers of apoptosis.

906-Pos Board B706
Robustness Portraits of Diverse Biological Networks Conserved Despite Order-Of-Magnitude Parameter Variation
Ananth S. Sridharan, Allan F. J. Saucerman

Many biological networks are robust to a wide variety of internal and external perturbations, yet fragile to a select group of uncommon perturbations. Because fragile system modes are highly sensitive to certain biochemical parameters, it is unclear how precisely biochemical parameters must be known in order to accurately predict the robustness portrait of a system. Here, we examined a previously well-characterized model of the cardiac beta-adrenergic signaling network [1-3] and found that the robustness portrait was well conserved, even when parameters were rounded to their nearest 1-2 orders of magnitude (r = 0.82 and 0.63, respectively). This analysis was then extended to 10 additional networks of diverse biological processes, including E. Coli chemotaxis, stem cell differentiation, and cytokine signaling. Nine out of 10 of these networks exhibited conserved robustness portraits (r > 0.75) despite systematic order-of-magnitude variations in their biochemical parameters. These results illustrate the ability to predict both fragile and robust aspects of diverse biological networks despite imprecise biochemical parameters. Additionally, this work suggests a strategy from which approximate models can be used to prioritize experiments towards fragile system modes, leading to efficient model validation and revision.

907-Pos Board B707
A mathematical Model of Signaling in Podocyte Foot Processes
Cibele V. Falkenberg, Michael L. Blinov, Leslie M. Loew

The first stage of blood filtration occurs in the glomerulus, where water and other small sized molecules are freely filtered into the urinary space while albumin and larger proteins are retained in the blood capillaries. Maintenance of the size-selective glomerular filtration barrier is regulated by highly differentiated cells, podocytes, their cell-cell interactions in the slit diaphragm and the cell-GBM (glomerular basement membrane) interaction of the podocyte foot processes. Mutations of the nephrin gene (NPHS1) triggers actin reorganization, loss of the podocyte functional morphology and massive proteinuria. The glomerular tissue is challenging to study in vitro, because podocytes from isolated glomeruli undergo de-differentiation within hours, while cultures of stabilized cell lines never complete differentiation. Therefore, to provide insight into how the integrity of the filtration barrier is dynamically maintained, we have developed a mathematical model of the podocyte that preserves the spatial organization found in the intact glomerulus, focusing on the nephrin pathway.

908-Pos Board B708
Is Intracellular pH a Master Clock for the Events of Mitosis?
Lucian J. Gagliardi

Experiments have shown that the intracellular pH of many cell types rises to a maximum at the onset of mitosis, subsequently decreasing 0.3 to 0.5 pH units from typical peak values of 7.3 to 7.5 measured during prophase [1]. This result, and observations that tubulin net charge depends strongly on pH, varying quite linearly from -12 to -28 (electron charges) between pH 5.5 and 8.0 [2,3], could be significant for microtubule (MT) dynamics during mitosis. Studies have shown that MT dynamics is sensitive to pH, with MT growth favored by higher intracellular pH values [4-6]. Given the above observations collectively, it seems reasonable to assume that the shift from the dominance of MT growth during prophase, and to a lesser extent during prometaphase, to a parity between MT polymerization and depolymerization during metaphase chromosome oscillations could be attributed to the gradual downward intracellular pH shift during mitosis that is observed in many cells. Thus the timing and sequencing of prophase, prometaphase, and metaphase chromosome motions may be understood as an increase in the MT disassembly to assembly probability ratio resulting from a continuously falling intracellular pH [7,8].


909-Pos Board B709
Noise and Crosstalk in the Two Quorum Sensing Channels of Vibrio Fischeri
Stephen J. Hagen, Pablo Delfino Perez, Joel T. Weiss

Bacteria use the signaling mechanism known as quorum sensing (QS) to detect and respond to their population density. By releasing a diffusible molecule (an 'autoinducer') into their environment, they can use the local concentration of this molecule as an indicator of population density and regulate phenotype accordingly. In many bacterial species the QS regulatory pathways are complex, receiving inputs from several different autoinducers. Therefore it is important to understand how bacteria integrate multiple signals and how the signal-to-noise property of each autoinducer channel affects that of other channels.

We have studied the role of noise and crosstalk between two QS signals in Vibrio fischeri, a luminescence bacterium that colonizes the light organ of a number of fish and squid species. V. fischeri produces a 3-oxo-C6 homoserine lactone autoinducer (3OC6HSL) that interacts with its receptor LuxR to activate transcription of the lux bioluminescence genes; the bacterium also produces a C8 homoserine lactone signal (C8HSL) that regulates aspects of host colonization. However, the 3OC6HSL regulation of lux is not only noisy at the single cell level, but is also subject to strong interference or crosstalk from the C8HSL signal. C8HSL indirectly activates the expression of LuxR while also competitively inhibiting the interaction of 3OC6HSL with LuxR.

We are investigating the effect of crosstalk between 3OC6HSL and C8HSL channels on the noise and sensitivity of the quorum response of individual V. fischeri cells. We use a microfluidic approach, where the cells occupy a microscopic chamber in which a continuous flow of medium imposes well-defined gradients and concentrations of exogenous C6HSL and C8HSL autoinducers. Using a chromosomal gfp reporter for the lux genes we can observe the joint effect of C8HSL and 3OC6HSL on quorum regulation and its temporal and cell-to-cell variability.

910-Pos Board B710
A LEGI-Biased Excitable Network Controls Temporal and Spatial Responses to Chemotactrants
Yuan Xiong, Chuan-Hsiang Huang, Pablo A. Iglesias, Peter N. Devreotes

Many cells have the ability to respond to external chemical stimulus, a process referred to as chemotaxis. Critical for many biological and physiological processes, the overall pathways that regulate chemotaxis are evolutionarily conserved, and the chemotactic behavior is similar among most eukaryotic cells. While there are no chemical cues, cells migrate randomly. Upon spatially uniform constant stimulus, they stop and round up, and localized patches of activity appear later as cells spread. Finally cells adapt and resume random migration. On the other hand, when exposed to a gradient of chemotactractant, cells are able to continuously steer their pseudopodia activity, thus their motility, toward the higher side.

Many models have been developed and can capture some features of chemotaxis, but none has brought together the diverse observations into a unified scheme. Here we propose the local-excitation, global-inhibition (LEGI) biased excitable network hypothesis, and formulate a model that simulates most of the temporal and spatial responses to chemotactrants. More specifically, our model couples the LEGI mechanism, which can partly predict the responses to step and gradient stimuli, with a downstream reaction-diffusion based noise-driven excitable system, which is simplified as a two-component activator-inhibitor model that controls the cytoskeletal activity. This LEGI-biased excitable network can explain the complex response kinetics, the sensitivity to shallow gradients, and the recently observed propagating waves of various molecular components in chemotaxing cells. Furthermore, by perturbing model parameters, our model is able to generate distinct behaviors consistent with known classes of mutant chemotactic cells.

Our model provides a framework to understand how newly appreciated excitable behavior in cells can be regulated by external cues and satisfactorily accounts for most of the responses of chemotactic cells to spatial and temporal stimuli, as well as motivate experimentations and interpret new observations.