0.8, 20, 40, 80 mM MgCl2 or CaCl2 preserved their integrity. Furthermore, the mere addition of MgCl2 or CaCl2 at the above concentrations to the external medium also resulted in preserved vesicles. Slightly flattened liposomes with heights ranging between 30 and 80 nm were observed on the surface, but ruptured, completely flattened vesicles were unseen. In the absence of divalent cations we observed the coalescence of flat, micrometer-size patches of lipid bilayers. If divalent cations were removed from the external medium by size exclusion chromatography, vesicle-integrity dramatically decreased. To test the effect of amyloid on liposome structure, transthyretin sample containing a variety of aggregates were added to surface-adsorbed vesicles. Upon the addition of transthyretin, liposomes immediately ruptured and flattened.
Our results demonstrate that surface-adsorbed liposomes stabilized with divalent cations represent a unique experimental system that may provide novel insights into the mechanisms of membrane-protein interactions.

900-Pos Board B700
DNA Condensation Revisited: Spermidine-Induced Novel DNA Networks on Mica Surfaces
Preethi Chandran, **Emilios Dimitriadis**, Ferenc Horkay.
Spermidine, a trivalent polyamine cation, is ubiquitously present in the cytoplasm of cells. Under low ionic concentrations, spermidine condenses DNA into dense structures, which have been studied to understand the packaging of viral DNA. Spermidine and other naturally occurring polyamines play important roles in DNA stability, and gene transcription regulation. Earlier studies on DNA condensation with spermidine have reported the formation of rods, globular structures and toroid-like formations. We report for the first time, the formation of DNA network condensates induced by spermidine. The networks were formed on mica surfaces and involve hierarchical structures of parallel and coiled DNA fibers. Atomic force microscopy (AFM) imaging of the networks show a rich pattern of DNA fiber branching. The networks arise under certain combinations of DNA to spermidine concentration ratios and incubation times. These structures originate in solution where spermidine can induce multiple DNA molecules to coil around each other. Under most conditions, consistent with previous studies, DNA is seen forming tight globular structures that aggregate to form more complex branched structures, rods and partial toroids. The variety of observed structures and the sensitivity of the condensation pathway to concentration ratios and incubation times points to as yet unexplored regions in the DNA condensation phase diagram.

901-Pos Board B701
Biological Atomic Force Microscopic Imaging and Force Spectroscopy of Protein Constructs as Potential Anti-Malaria Vaccines
Svetlana Kotova, Joanna P. Rys, Mai-Ann Tran, Paul D. Smith, Darrell E. Hurt, Jack Lebowitz, David L. Narum, **Albert J. Jin**.
Atomic force microscope (AFM) is quickly becoming a general nano-characterization tool for biomedical samples. Here we have used AFM imaging and single molecular force spectroscopy to characterize leading malaria vaccine candidates that are various recombinant forms of Plasmodium falciparum circumsporozoite protein (Plassmeyer, M., et al., 2009. J. Bio. Chem., 284:26951-63)). We have achieved high-resolution AFM single molecule imaging and force spectroscopy of these important antigens under various buffer and surface deposition conditions to better understand the recombinant protein constructs. The protein folding domains and tertiary structure features observed from AFM imaging and deduced from AFM force spectroscopy are closely correlated with accurate computational structural predictions derived from the primary sequences and bulk solution characterizations. Bio-AFM characterizations can discriminate alternative forms of recombinant proteins according to their oligomerization and surface presentations. Our results showcase AFM as an insightful tool of nanomedicine for in-depth understanding of single proteins and protein-protein interactions.

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902-Pos Board B702
Computational Analysis of the TGF-Beta and BMP Signal Transduction Pathways
Jonathan Ho, Leonor Saiz.
The TGF-beta and BMP signaling pathways transduce extracellular signals into transcriptional responses affecting key cellular processes, including cell growth, apoptosis, proliferation, differentiation, and morphogenesis. Defects within the signaling pathway have been correlated with many diseases, both developmental and chronic. Here, we present a computational analysis of a model for TGF-beta and BMP signaling pathways that includes macromolecular assembly, receptor trafficking and signaling, nucleo-cytoplasmic shuttling of smad-complexes, and feed-back through the products of regulation of gene expression. We study the dynamics of the systems and identify the key parameters, and cellular processes, 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, Yasuhiko 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 V_m-dependent Ca^{2+} current (I_{CaL}) 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 (EPs), 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, John C. Chappell, Alex Nguyen, Shayn 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