Brownian Dynamics and Monte Carlo simulations, allowing us to integrate molecular-scale information, such as the shapes and sizes of each molecular species, into the rate equations of the model. The steady state cytoplasmic mRNA concentration shows several regimes with qualitatively different dependencies on the volume fraction \( \phi \cdot \phi \) of crowding agents, depending on the concentrations of the transcription factors, polymerases, and DNA binding sites. At physiologically realistic volume fractions, the mRNA output may be an increasing, decreasing, or non-monotonic function of \( \phi \cdot \phi \) in these various regimes. Our results suggest that the transcriptional output of a gene can be regulated jointly by the local level of macromolecular crowding, together with the local concentrations of polymerases and DNA-binding proteins.

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**1906-Pos Board B636**

**Crosstalk and the Evolution of Specificity in Two-Component Signaling**

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Two-component Signaling (TCS) serves as the dominant signaling modality in bacteria. A typical pathway includes a sensor Histidine Kinase (HK) that phosphorylates a Response Regulator (RR), modulating its activity in response to an incoming signal. Most HKs are bifunctional, acting as both kinase and phosphatase for their substrates. Unlike eukaryotic signaling networks, there is very little crosstalk between bacterial TCS pathways; indeed, adding crosstalk to a pathway can have disastrous consequences for cell fitness. It is currently unclear exactly what feature of TCS necessitates this degree of pathway isolation. In this work, we developed a mathematical model to show that the features of bifunctional HKs, adding a competing substrate to a TCS pathway will always reduce response of that pathway to incoming signals. We found that the pressure to maintain cognate signaling is sufficient to explain the experimentally observed “kinetic preference” of HKs for their cognate RRs. These findings imply a barrier to the evolution of new HK-RR pairs, since crosstalk is unavoidable immediately after the duplication of an existing pathway. We characterized a set of “near-neutral” evolutionary trajectories that minimize the impact of crosstalk on the function of the parental pathway. These trajectories predicted that crosstalk interactions should be removed before new input/output functionalities evolve. Analysis of HK sequences in bacterial genomes provided evidence that the selective pressures on the HK-RR interface are different from those experienced by the input domain immediately after duplication. This work thus provides a unifying explanation for the evolution of specificity in TCS networks.

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**Heterogeneous Protein-Protein Interaction Systems Modeled using a New Integrator for Single-Particle Reaction Diffusion**

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Proteins perform functions ranging from signal transmission and transcriptional regulation to assembly into structural scaffolds by stochastically binding with one another in the cellular environment. Approaches to modeling these processes at a scale capable of capturing the dynamics of whole populations of proteins vary in the degree of spatial resolution and the rules describing the interactions between proteins. We present here a new algorithm for simulating both the spatial and temporal evolution of protein interactions by rigorously solving reaction-diffusion equations at single-particle resolution. Our algorithm is designed to be both highly accurate and relatively simple to implement, making it applicable to large and heterogeneous systems, including those arising in systems biology applications. In our approach we combine the use of the exact Green’s function for a pair of reacting particles with the approximate free diffusion propagator for position updates to particles. Through the use of a trajectory reweighting scheme our method recovers the exact association rates for a pair of interacting particles at all times. As a result, simulations of many-body systems with our method quite accurately reproduce the theoretically known dynamic behavior for a variety of different reaction types. This approach has applications in modeling pathways and networks of protein driven processes where reactions can range widely in strength and thousands of proteins may participate. With a limited amount of bookkeeping necessary to ensure proper association rates for each reactant pair, our approach can adapt to changes in reaction rates or diffusion constants as a result of reaction events. The formalism can also be extended to physical descriptions of protein interactions that incorporate long-range forces or orientational constraints, providing a framework to help bridge the gap between molecular models and particle-based models of protein interactions.

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**Computational Model for Cell Shape Regulation through Mechanosensing and Mechanical Feedback**


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In response to both intracellular and extracellular signals, cells undergo controlled changes in morphology, which form a fundamental step in many developmental processes, including tissue morphogenesis and organogenesis. These changes require a means for sensing and interpreting the signaling cues, for generating the forces that act on the cell’s physical material, and a control system that regulates this process. Identifying the molecular mechanisms that drive and regulate cell shape changes is a great challenge in the field of cell biology.

In studies of dividing Dictyostelium discoideum amoebae, it has been shown that force-generating proteins could be localized in response to external mechanical perturbations. This mechanosensing, and the ensuing mechanical feedback, is believed to play an important role in minimizing the effect of mechanical disturbances during cell division. Owing to the complexity of the feedback system, which couples mechanical and biochemical signals involved in shape regulation, it is essential to develop theoretical approaches that can guide future experimentation and modeling efforts. Here, we present a mechano-chemical computational model that explains the different mechanosensory and mechanoresponsive behaviors observed in Dictyostelium cells. This model expands a multi-scale myosin bipolar thick filament assembly model that incorporates cooperative and force-dependent myosin-actin binding, by identifying the feedback mechanisms hidden in the observed mechanosensitive processes at a scale capable of capturing the dynamics of whole populations of proteins.

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**Stochastic Modelling of Gene Regulatory Mechanisms in PTEN Dynamics: Does Space Matter?**

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Stochastic simulation has proven to be an invaluable tool for modelling biological processes involving small numbers of molecules, such as proteins and messenger RNA (mRNA). One aspect of sub-cellular dynamics that is often overlooked in stochastic models is the effect of spatial constraints on the behaviour of a cell; cellular processes depend not only on the number of molecules present, but also on their distribution, how they move within the cell and how they interact with each other. This type of modelling is particularly relevant in crowded media such as the cytoplasm, which is filled with organelles and other molecules. For these reasons, we hypothesise that spatially-resolved models of cells will prove to be more effective at simulating the behaviour of individual cells than spatially-averaged ones. To test this hypothesis, we studied the regulation of the mRNA of the tumour suppressor gene, PTEN, by a group of small RNAs called microRNAs. We created spatially-resolved models of the system using Smoldyn, a discrete-time, continuous-space, agent-based spatial stochastic simulation tool, and compared the results with those obtained using the spatially-averaged stochastic simulation algorithm (SSA). We measured the average time for an mRNA to be degraded or repressed by a threshold number of microRNA, and investigated the change in this mean time with the inclusion of cytoplasmic obstructions, non-uniform distributions of molecules, and competition for binding by competing endogenous RNAs (ecRNAs). Preliminary results demonstrate a considerable impact of spatial modelling on observed cellular response times, as we see a dramatic increase (>100-fold) in the time taken for microRNAs to locate mRNA binding sites in the spatially-resolved model.

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**1910-Pos Board B640**

**Bacterial Growth and Division: Theory**

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Minimal models reveal principles behind cellular functions, such as, what biochemical rules underlie growth limits? how ribosomes and metabolic proteins compete for energy resources? how are efficiency of conversion of energy to mass compete with growth rate following economic principles? To address