null-mutants and over-expression transgenic animals for CPX and SYT at the Drosophila NMJ. Genetic interaction and kinetics analysis reveals that CPX and SYT expression modulate the rates of spontaneous and synchronous/asynchronous release. Additionally, SYT and CPX levels alter vesicle delivery during tetanic stimulation. Our finding indicate that different levels of SYT and CPX have computational consequences at nerve terminal that modulate basal noise, output gain, speed of transmission and the short-term plasticity.

PLATEFORM N: Regulatory Networks & Systems Biology

164-Plat

Construct and Simulate Virtual Cell with Minimum Genome at the Nanoscale
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Understanding the design principles of living systems at the nanoscale presents both challenge and promise for controlling cancer cell. We constructed and simulated a virtual cell model containing 206 proteins in the minimal bacterial genome. All the molecules are treated as nano-scale spheres. The short-range attraction interactions between those macromolecules are described by the Lennard-Jones potential, and electrostatic interactions by the point charge model. The motion of the protein particles are simulated with Langevin Dynamics. 8 copies of the Green Fluorescent Proteins are also described by the Lennard-Jones potential, point charges, and viscosity of the cytoplasm), we reproduced the experimental diffusing constant for GFP. We found that in virtual cell simulation, the selection of protein and their concentration are very important to represent cellular life. The spatial and temporal distributions of cytoplasmic proteins are not homogenous. The hierarchical protein clusters may provide spatial pathways for protein-protein interaction networks. This project has been funded by the NCI, contract number HHSN261200800001E.

165-Plat

Toward a Whole Cell Model of Mycoplasma Genitalium
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A central challenge in biology is to understand how cellular life emerges from individual biochemical interactions. To address this challenge we have developed a novel computational framework which facilitates the integration of multiple disparate biochemical networks and data into a single unified model. Using this framework we have developed a detailed computational model of the complete life cycle of the smallest known freely-living organism, Mycoplasma genitalium. The model describes the life cycle of a single cell including DNA, RNA, and protein synthesis, metabolism, and cell division. The model accounts for the specific function of every annotated gene product, and simulates the dynamics of every molecular species. We have validated the model using several publicly available experimental datasets. Currently we are using the model to gain insight into the control and regulation of cellular growth by exploring the effects of genomics and environmental perturbations on cellular behavior. In addition, we are developing an open-source, open-access web-based platform to facilitate broad applications of our model.

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Non-specific Binding Limits the Number of Proteins in a Cell and Shapes their Interaction Networks
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Multicellular organisms, from the simple worm to humans, have roughly the same number (about 20,000) of protein encoding genes. We find that the need to prevent disease-causing non-specific interactions between proteins provides a simple physical reason why organism complexity is not reflected in the number of distinct proteins. Through computational evolution of the amino-acid sequences of protein binding interfaces with an empirical energy function, we quantify the degree of mix-binding as a function of the number of distinct proteins. We show that the achievable energy gap favoring specific over non-specific binding decreases with protein number in a power-law fashion. We demonstrate how the scaling of this power law depends on the size of the binding interfaces and the topology of the protein interaction network. We predict the limits these binding requirements place on the number of different proteins that can function effectively in a given cellular compartment by calculating the fraction of proteins involved in non-specific complexes as a function of increasing protein number and decreasing energy gap. Remarkably, the optimization of interfaces favors networks in which a few proteins have many partners, and most proteins have few partners, consistent with a scale-free network topology. We conclude that non-specific binding adds to the evolutionary pressure to develop scale-free protein-protein interaction networks.

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Exact Identification of Topologically Essential Interactions in the Networks Derived from Perturbation Experiments
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Perturbation screens (e.g. by gene knock-downs) are one of the most promising tools available for discovering the structure of complex biological networks. Considerable obstacle in understanding the results of such screens stems from inability to distinguish the indirect effects of a perturbation from the direct effects. Thus, networks derived from typical perturbation screen are significantly more complex than true underlying networks. The problem of identifying a minimal core network topology consistent with results of perturbation screen (i.e. discriminating between direct and indirect effects of a perturbation) has been accurately formulated previously but despite the attempts to solve it, only approximate methods with severe limitations have been developed. Here, we report a novel approach that is based on the theory of self-avoiding random walks which allows one to find an exact solution to the problem: given experimentally derived network one can identify core network(s) consistent with original network (note that for sufficiently complex network, more than one core network is possible). By introducing novel matrix representation of the network topology we reduce the problem of identifying core underlying networks to the counting of self-avoiding random walks in the original network, thus allowing exact solution for any input network topology. We describe application of our approach to synthetic data obtained by simulating artifically constructed networks, as well as to the results of real perturbation screens performed in yeast and mammalian systems.

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Detection of Predictive Dynamics of Glucocorticoid Receptors in Xenopus Laevis Embryonic Tissues
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The regulatory interactions in embryonic development that is guided by a complex set of spatially and temporally integrated stimuli result in the emergence of highly functional units. Since a better understanding of spatiotemporal responses provides a great insight to fundamental emergent patterns that may evolve from complex systems such as embryonic development, it is important to examine a generalized response to frequency-modulated stimulation from a system comprised of hundreds of cells where each cell has millions of interacting molecules. We present the dynamic responses of vertebrate embryonic tissues to time-varying localized chemical stimulation through a closed-loop microfluidic control that enabled localized spatiotemporal regulation of steroid hormone dexamethasone (DEX) in Animal Cap (AC) tissues isolated from gas-trulating Xenopus embryos. We investigated dynamic cell-scale responses to precisely controlled stimulation by tracking the activity of a GFP-tagged Glucocorticoid Receptor (GR). Interestingly, the overall response had a predictive first-order behavior to periodic stimulation environments. We modeled these dynamic responses using first order differential equation with two different time derivatives: moving into and out of the nucleus. There was a good agreement between the predicted responses and the experimental results. Our approach provided a methodology for manipulating these biochemical inputs to examine and model the collective behavior of many biochemical reactions. The intricate cellular signaling and transport machinery responses were similar to behaviors in other complex systems, suggesting that even within a highly integrated and robust embryonic tissue, the overall system that we had studied converged toward a predictive first-order response. We believe that our results may suggest in the future that nanoscale molecular interactions in this developmental system results in highly regulated behavior, which we are able to determine through our feedback microfluidic control approaches in developmental biology.