3847-Pos
Cholesky-Langevin Model for Biochemical Networks with Accurate Account of Stochastic Effects of Couplings between Molecular Species
Youfang Cao[1,2], Jie Liang[1,2].
[1]Shanghai Center for Systems Biomedicine, Shanghai Jiao Tong University, Shanghai, China, [2]Department of Bioengineering, University of Illinois at Chicago, Chicago, IL, USA.
The dynamics of stochastic biochemical networks are often modeled using Langevin equations as an approximation to the underlying Chemical Master Equation. However, the coupling effects between different molecular species are neglected in current Langevin models. These coupling effects are important when intrinsic stochasticity due to the small-copy number nature and the discrete nature of the reactions system is non-negligible. Here we develop a generalized Langevin approach, called the Cholesky-Langevin Model (CLM), to incorporate rigorously both the fluctuations of chemical species and the stochasticity of their pairwise-coupling effects. We exploit the property of positive semi-definiteness of the stochastic covariance structure of a biochemical network of arbitrary stoichiometry. By comparing the calculated probabilistic landscapes using CLM with that from the conventional Langevin Model and the exact landscape obtained by directly solving the Chemical Master Equation using a method recently developed in (Cao and Liang, 2008), we show through several examples that the CLM model significantly improves the accuracy in approximating the underlying Chemical Master Equation. This study shows the importance of the coupling effects between molecular species in biochemical networks, and points out an effective approach for their rigorous account. We also discuss the biological implications of our approach. (Cao and Liang, BMC Systems Biology 2008, 2:30)

3848-Pos
Predicting the Toggle Switch Bistability from Maximum Uncertainty Principles
Steve Presse[1], Kingshuk Ghosh[2], Ken A. Dill[1].
[1]U.C.S.F., San Francisco, CA, USA, [2]University of Denver, Denver, CO, USA.
The toggle switch is a double negative feedback loop involving production of mutually repressing transcription factors. In small systems, fluctuations in transcription factor production give rise to steady state bistability. Here we invoke a dynamical extremum principle, Maximum Caliber, which we use to predict transcription factor production fluctuations and steady state switching behavior. Maximum Caliber models have no adjustable parameter, rather the modeling relies on available experimental averages used as constraints to describe the stochastic system dynamics. We demonstrate how this method can be used to analyze experimental data and discuss its generalizability to more complicated problems.

3849-Pos
On the Equivalence of the Equilibrium Correlation and Non-Equilibrium Response in Stochastic Biochemical Kinetics
Chao-Ping (Cherri) Hsu, Ching-Cher Sanders Yan.
Academia Sinica, Taipei, Taiwan.
The response of a cell to an external perturbation to its biochemical state shows how it cope or adapt to such changes. It is a useful way to probe many features of the system, including the timescales of resonances and relaxation processes. The Fluctuation-Dissipation theorem (FDT) is desirable to extend the scope of the response observed. In a thermodynamic system, the response is determined by the statistics of the Hamiltonian, and the FDT allows us to connect the response function to the correlation function in an equilibrium state. In thermodynamics, the microscopic trajectories are determined by the Hamiltonian of the system, and the ergodic assumption allows the statistical treatment for the macroscopic observables. On the other hand, systems in stochastic chemical kinetics can be regarded as a Markovian processe that follows a master equation. Trajectories in a multidimensional space spanned by the numbers of molecules of all species evolve by chemical reactions, which take place under the reaction probability determined by the rate constants, instead of a deterministic Hamiltonian. Many fundamental developments in the stochastic chemical kinetics are very similar to that for thermodynamics, and therefore, FDT is intuitively plausible for stochastic chemical kinetics.
In the present work, we established the FDT for stochastic chemical kinetics and verified it numerically. The response functions in both time and frequency domains were calculated and analyzed. Our work allows a connection between the nonequilibrium responses of the system and the equilibrium, stochastically based correlation functions. The capacity of probing dynamical characteristics from the response function is also explored.

3850-Pos
Modularity and Centrality in Metabolic Network Evolution
Craig C. Jolley, Aurélien Mazurie, Mark Young, Trevor Douglas.
Montana State University, Bozeman, MT, USA.
Large-scale genome sequencing and annotation projects have led to the construction of detailed small-molecule metabolic networks for a variety of organisms. When the large-scale topological features of metabolic networks are compared across species, several evolutionary trends emerge, impacting the networks'size, modularity, and degree of central organization. Metabolic networks have been shown to exhibit scale-free topology, which can be created through processes of growth and preferential attachment. We present preliminary results on a kinetic Monte Carlo model, in which evolutionary changes result from gene duplication and enzyme active site mutation events. The evolutionary dynamics are driven by a flux-based fitness function which can be used to represent different environmental constraints.

3851-Pos
Using Effective Empirical Sub-Networks to Move Equilibria of Gene Networks
Gemunu Gunaratne.
University of Houston, Houston, TX, USA.
Many biological processes are governed by the action of networks of genes, proteins, and other molecules. We ask how the equilibrium of such a gene network $\calN_0$ can be moved from an initial, perhaps undesirable, state $\exists \calP_0$ to a pre-determined state $\calP_{aim}$ through external (pharmacological) intervention. The input for our analyses are the expression levels of genes in $\calP_0$ and $\calP_{aim}$, as well as those of sets of their genetic perturbations.
We first find genes that are differentially expressed between the two groups, and partition them into clusters that are weakly coupled to each other. Since genes within cluster are strongly coupled, their expression levels change coherently between genetic perturbations. We asume that all genes within a cluster can be moved by appropriate changes in a few. We thus construct a subset $\calN_S$ that contains a small number of genes from each cluster. We next show how ''effective'' interactions between nodes of $\calN_S$ can be computed using expression levels of genes in $\calP_0$ and all its single knockout mutants. We argue that geometrical constraints imposed by the construction makes the solutions of $\calN_S$ close to those of $\calN_0$. This proximity of solutions allows us to compute how the equilibrium can be moved from $\calP_0$ to, or as close as possible to, $\calP_{aim}$.

3852-Pos
Investigating Co-Regulation Networks using Generative Models
Matthew B. Carson[1], Nitin Bhardwaj[2], Hui Lu[1].
[1]University of Illinois at Chicago, Chicago, IL, USA, [2]Yale University, New Haven, CT, USA.
Proteins, often referred to as the 'workhorses of the cell';, are produced through the process of gene expression, during which an organism turns its genetic code (DNA) into functional units. Regulation of this expression process increases the versatility of an organism, allows for adaptation to the environment, and in-creases the efficiency with which resources are metabolized by controlling when and in what quantities RNA molecules and proteins are pro-duced. Many diseases are related to failures in one or more components of this system. Examining regulation helps us to understand how an organism evolves and develops, and how malfunctions may break down this process. Much of the control of gene expression is believed to occur by the cell's adjustment of tran-scription initiation frequency. This level of control is carried out by transcription factors (TFs), and transcription factor networks (TFNs) can be used to describe the interactions between these transcription factors and their target genes. In this work we use generative networks to model the creation of TFNs during evolution in order to understand how these networks form and develop. In par-ticular, we examine how the number of TF partners (those that regulate common genes) scales with the number of genes a TF regulates. It has been observed that in several model organisms the degree distribution of this partnership net-work appears to follow an exponential saturation curve. The co-regulatory net-work of our generative model shows a trend similar to that of the model organ-isms. We show that through various modifications to our model we are able to identify the necessary conditions for this observed saturation curve characteristic. This indicates that the saturation curve seen in these co-regulatory networks could be a product of evolutionary development, during which regulators gain and lose interactions with targets over time.