

911-Pos Board B711**Topological Properties and Variations of Cells in Proliferating Epithelia: Impact of Mechanical Force and Division Orientation**
Yingzi Li, Hammad Naveed, Sema Kachalo, Jie Liang.

Proliferating epithelia are sheets of dividing cells that tightly adhere to each other in many metazoans. Regulation of cell division is important for both normal and diseased epithelia. Quantitative analysis of epithelia shows significant conservation in the dominance of hexagonal cells in both animal and plant. However, there exist species with significant varied amount of hexagonal cells. The mechanism controlling these distributions is poorly understood. In this study, we use a computational method called cellGPS (cell global pattern simulator) to study the dynamic process of proliferating epithelia based on a mechanical off-lattice cellular model. This method keeps track of full geometric and biomechanical properties of epithelia. It models cell shape, area, perimeters and surface tension. Two biologically relevant division rules, namely, the orthogonal orientation found in plants and the largest-side orientation found in the mitotic spindle in human cells, are also incorporated in the division process. With this method, we found that regardless of division rules, our mechanical model can produce the common epithelia pattern of the dominance of hexagonal cells. In addition, we found that division rule of largest-side orientation lead to the formation of cell pattern with around 45% hexagons, which is observed in many animal epithelia and some plant tissues. This suggests that reducing stress on the cell wall by dividing the largest side is widely used in animal epithelia. The percentage of hexagons from division following orthogonal orientation is found to be about 60%, consistent with observations found in certain plant tissues. We conclude that both mechanical force and division orientation play important roles during epithelial proliferation. Mechanical model itself leads to topological dominance of hexagonal cells, and different rules of division orientation lead to varying amount of hexagonal cells.

912-Pos Board B712**Functional Roles of Slow Enzyme Conformational Changes in Network Dynamics****Zhanghan Wu, Jianhua Xing.**

Extensive studies from different fields reveal that many macromolecules, especially enzymes show slow transitions among different conformations. The phenomenon is named as dynamic disorder, hysteretic and mnemonic enzymes in different fields, and is directly demonstrated by single molecule enzymology studies. We analyzed enzyme slow conformational changes in the context of regulatory networks. A single enzymatic reaction with slow conformational changes can be noise buffer filtering upstream fluctuations, shows resonance and adaptation, and thus serves as a basic functional motif with properties normally discussed with larger networks in the field of systems biology. We further analyzed examples including enzymes functioning against pH fluctuations, metabolic state change of *Artemia* embryos, kinetic insulation of fluctuations in metabolic networks, and possible synthetic networks with various properties. The work fills the missing gap between studies on intramolecular and network dynamics.

913-Pos Board B713**Theoretical Modeling of Bi-Connected Elementary Biochemical Reaction Cycles****Tatsunori Nishimura, Masaru Tateno.**

In most cases, computational models of biochemical reaction networks are described using time-dependent ordinary differential equations (ODEs). However, to obtain the cellular response when the system is in a steady state, which is closely relevant to various crucial phenotypic events, ODEs can be converted to time-independent algebraic equations. By exploiting the solutions of the equations, the relationships between the strength of an extracellular signal and the magnitude of the cellular response (i.e., the stimulus/response relationship) are obtained. In this study, we investigated the dependence between the number of solutions (the multistability) of the equations and the gradient of the inflection point (steepness) of the stimulus/response curve on a kinetic parameter space, which was defined by the ratios of the catalytic efficiency (referred to as λ_1 and λ_2) of bi-connected elementary cellular reaction cycles, composed of a substrate and two enzymes. As a result, we found that, when λ_2 was initially small and then increased (λ_1 was fixed), the steepness also increased, leading to the monostability to bistability transition. This was the case with the λ_1 axis, although, when λ_1 increased (λ_2 was fixed), the steepness decreased, resulting in the bistability to monostability transition. This is the first report to systematically show that the steepness is closely correlated with the stability of the elementary cellular reaction systems. Furthermore, the effects of a positive feedback loop (PFL) upon the responses of a bi-connected elementary reaction cycles were investigated by exploring the stability of the steady state

equations. We found that the origin of the bistability to monostability transition, which had not been found previously, was the significantly lower Michaelis-Menten constant in the PFL, leading to the sequestration of the substrate through the tight binding of the enzyme and substrate.

914-Pos Board B714**Modeling Alzheimer's Disease using a Systems Biology Approach**
Christina R. Kyrtos, John S. Baras.

Alzheimer's disease (AD) is the most common form of dementia afflicting the elderly today and is believed to be caused by the buildup of the beta amyloid protein (A β) within the brain and cerebral vasculature. Although a vast amount of knowledge exists, there is currently no definitive understanding of the initiating factor and subsequent pathogenesis, partially due to the difficulty in directly studying or manipulating the brain experimentally. To overcome this problem, we have developed a systems-level network that encompasses metabolic, lipidomic, and proteomic network topologies, taking into account known feedback and regulation mechanisms. By studying the interactions between the different networks computationally, we have identified several nodes which may be key for initiating a change from a "healthy" network state to a "disease" state. We have also performed *in vivo* experiments in APP/Swe/PS1 transgenic mice to study the effect of simvastatin, a cholesterol inhibitor and potent anti-inflammatory, on the expression levels of A β , APP, LRP-1 and apoE. These experiments, in combination with our computational model, help to identify crucial feedback points and provide the first known attempt to model AD from a systems-level standpoint.

915-Pos Board B715**Bipartite Network Analysis of (bio)CHEMICAL Reaction Systems**
Craig C. Jolley, Trevor Douglas.

Complex chemical reaction networks are most naturally represented as graphs that are bipartite (i.e. contain two classes of nodes for reactions and chemical species) and directed (i.e. have edges that point from reactants to reactions and reactions to products). Traditionally, the starting point in the network-theoretical analysis of chemical reaction systems has been the projection of this directed bipartite graph to an undirected unipartite graph containing only chemical species. We are developing projection-free methods for the analysis of complete bipartite directed networks which allow us to separate the roles of reactions and chemical species in determining large-scale graph structure. Consideration of the full unprojected network allows the identification of new types of network motifs (and anti-motifs) that distinguish chemical reaction systems from more general network models. This bipartite approach to chemical network analysis is applicable to a wide range of chemical systems, ranging from the metabolism of *E. coli* to gas-phase reactions in the interstellar medium. Such comparisons allow us to identify the characteristic differences between chemical reaction networks present in living and non-living systems.

916-Pos Board B716**Extracting Mechanistic Insight from Large Biochemical Networks via Statistical Analysis****Michael Dworkin, Sayak Mukherjee, Ciriya Jayaprakash, Jayajit Das.**

Hierarchical cell signaling and gene regulatory kinetic reactions, composed of rich biochemical networks, produce decisive functional outcomes in cells that interact with diverse stimuli. Recent developments in high throughput experiments provide us with detailed views of these complex phenomena. While the amount of data from such experiments containing enormous number of variables is impressive, it is difficult to extract mechanisms underlying the complex kinetics that determine functional outcomes. Elucidating the mechanisms is essential for both scientific understanding and therapeutic applications.

We study multivariate statistical methods (e.g., principal component analysis) based on covariances used in the analysis of high throughput data sets. We show that these lead to a dramatic reduction (from hundreds to fewer than 5) of the dimensionality in the time-dependent data obtained from numerical solution of coupled ordinary differential equations describing large, biologically significant sets of biochemical reactions. We find this reduction independent of the form of the nonlinear interactions, network architecture and over a wide range of parameter values (rate constants and concentrations). We show how changes in time scales in the system are associated with the relative changes in the number of the principal components required to capture the maximal variance in the data set. We provide examples where description of the system kinetics in terms of few principal components can lead to new insights into complex multi-dimensional systems. This may lead us toward uncovering mechanisms and identifying the key processes in complex biological systems.