and early genes are upregulated even at the lowest TNF-α concentrations, indicating digital signaling to gene expression. Late gene expression requires persistent NF-κB activity that is induced only at highest signal levels. The measurements reveal the activation threshold, a hypersensitive dynamic range and saturation, and shows that as few as two bound receptors can activate the pathway. The cells further encode TNF-α concentration information by modulating the temporal dynamics of NF-κB, with higher concentrations resulting in faster activation and more oscillations. Our results -in addition to their biological significance- highlight the importance of high-quality, high-throughput measurements at the single-cell level in understanding how biological systems operate.

2220-Plat

Quantitative Test for Mirror Symmetry Relationship between Sister Cells

Susanne Rafelski[1,2], Jacob Schroder[3,2], Carolina Torrealba[4,2], Melanie Mueller[5,2], Xiaolei Su[6,2], Monica Guo[1], Wallace Marshall[1,2], Ludovic Brun[7,2], Patrick Oakes[8,2], Julie Janvore[9,2], Qicong Hu[10,2], **Jennifer Hou[11,2]**.
[1]UCSF, San Francisco, CA, USA, [2]Marine Biological Laboratory Physiology Course, Woods Hole, MA, USA, [3]University of Copenhagen, Copenhagen, Denmark, [4]Pontificia Universidad Católica de Chile, Santiago, Chile, [5]Max Planck Institute, Potsdam, Germany, [6]Harvard Medical School, Boston, MA, USA, [7]European Molecular Biology Laboratory, Heidelberg, Germany, [8]University of Chicago, Chicago, IL, USA, [9]Institute Curie, Paris, France, [10]Stanford University, Palo Alto, CA, USA, [11]Harvard University, Cambridge, MA, USA.

Cell shape determination is a dynamical process modulated by input from genetic and signaling pathways. In order to understand cell morphology as a dynamical system it is critical to determine the degree of spatial inheritance, that is, the degree of influence of spatial organization within a mother cell on the organization of her daughter cells. Visual comparison of symmetry relations between daughters was used by Albrecht-Buehler to probe spatial inheritance in a series of papers published in the 1970's. His results, that sister cells are sometimes mirror images of each other, were interpreted as reflecting spatial inheritance during cell division. We have reinvestigated these claims using quantitative image analysis and several different shape-comparison algorithms to test the symmetry relations between sister cells. Applying these methods to fixed and live RPE-1 and NIH 3T3 cells, we obtained the following results: (A) sister cells are quantitatively more similar in shape than pairs of unrelated cells, (B) When sister cells show a significant degree of shape similarity, they tend to be related by mirror symmetry, (C) the shape similarity between sister cells is highest soon after division and decays on a time scale of several hours, (D) the set-theoretic union of the two sister cell shapes is related to the shape of the mother with a degree of similarity that decays as a function of time before and after division. We have also developed methodologies to compare similarity of internal actin stress fiber organization between sisters and to compare the migration trajectories of sister cells as they move away from the site of division.

2221-Plat

Tuning the Range and Stability of Multiple Phenotypic States with Coupled Positive-Negative Feedback Loops

Maier S. Avendaño[1], Chad Leidy[1], Alexander V. Oudenaarden[2], Juan M. Pedraza[3].
[1]Universidad de los Andes, Bogota, Colombia, [2]Massachusetts Institute of Technology, Cambridge, MA, USA, [3]Harvard Medical School, Boston, MA, USA.

The ability of a cell population to maintain simultaneously multiple phenotypic states is crucial for cell fitness. It is well known that the presence of a positive feedback is sufficient to generate multistability. However, many transcription networks contain counteracting positive and negative feedbacks, which indicates that this multiloop design provides additional advantages. Through an experimental and computational study in an interlinked positive and negative feedback motif in which each feedback strength is modulate independently, we explore the dynamic properties of this interlinked network. Our results show that the transition rates between different phenotypic states are not modulated by the positive, but only by the negative feedback strength. These results indicate that the negative feedback strength determines the phenotypic behavior of the cell populations, modulating the range and stability of different multistable states. By measuring noise levels in mRNA expression we show that this differential behavior is possible because noise levels are modulated independently by each feedback motif inside this genetic network. This suggests that in this coupled design, the strength of the negative feedback loop may be tuned to allow a population to enhance its fitness by changing the rate of stochastic transitions between different states, thus ensuring that cells may be prepared to confront a given level of environmental fluctuations.

2222-Plat

The Effects of Spatial Heterogeneity and in vivo Crowding on the Lac Genetic Circuit

Elijah Roberts, Andrew T. Magis, Zan Luthey-Schulten.
University of Illinois, Urbana, IL, USA.

Standard deterministic and stochastic models used to explore the dynamics of cellular biochemical networks typically ignore spatial degrees of freedom (by assuming the cell is well-stirred). Spatial heterogeneity has been neglected due to the lack of both data regarding cellular localization and computational methodologies to simulate such models. Advances in *in vivo* imaging techniques, including cryo-electron tomography and single-molecule fluorescence microscopy, have begun to reveal the organization and dynamics of biomolecules inside the cell. Likewise, graphics processing units (GPUs) now provide the computational power to perform three-dimensional simulations of cell-scale models. Here, the effects of incorporating spatial information and molecular crowding into a stochastic model of the lactose utilization genetic circuit are reported. We use our recently developed lattice-based Monte Carlo simulation technique [1] to sample the reaction-diffusion master equation describing the lac circuit in an *Escherichia coli* cell. Parameters are obtained from published *in vivo* single molecule studies. By comparing to the well-stirred model, it is shown that spatial degrees of freedom introduce a source of noise into the circuit. Such spatial noise is a component of the extrinsic noise of a genetic system and we put bounds on its contribution. In certain fluctuating environments, spatial noise is found to influence the switching properties of the circuit leading to population distributions that cannot be predicted using well-stirred models. Finally, the model suggests new single molecule experiments to probe the lac circuit and provides estimates of the spatial and temporal resolution required. The integration of lattice microbe models with systems biology descriptions of cellular networks is also discussed.

[1] Roberts, Stone, Sepulveda, Hwu, and Luthey-Schulten, ''Long time-scale simulations of *in vivo* diffusion using GPU hardware'', In *The Eighth IEEE International Workshop on High-Performance Computational Biology* (2009).

2223-Plat

Macroscopic Kinetic Effect of Cell-To-Cell Variation in Biochemical Reactions

Pan-Jun Kim, Nathan D. Price.
University of Illinois at Urbana-Champaign, Urbana, IL, USA.

Genetically identical cells under the same environmental conditions can show strong variations in molecular content such as in protein copy numbers due to inherent stochastic events in individual cells. We here develop a theoretical framework to address how variations in enzyme abundance affect the collective kinetics of metabolic reactions observed with a population of cells. Kinetic parameters measured at the cell population level are shown to be systematically deviated from those of single cells, even within populations of homogeneous parameters. The Michaelis-Menten kinetics, besides, can be destroyed at such population level. Our findings elucidate the novel origin of discrepancy between *in vivo* and *in vitro* kinetics, and offer the potential utility of single-cell metabolomic analysis.

2224-Plat

On Population Heterogeneity and Coexistence of Bacteria and Phage

Xiao-Lun Wu[1], Radu Moldovan[1,2].
[1]University of Pittsburgh, Pittsburgh, PA, USA, [2]Carnegie Mellon University, Pittsburgh, PA, USA.

Population dynamics experiments using bacterium Escherichia coli and phage lambda are carried out in a well-mixed environment. In all trials, the long-term behavior is the coexistence of the bacterial and the phage populations. This outcome is remarkably insensitive to various experimental conditions such as the initial bacterial population size and the initial infection ratio. Upon isolation of survival bactaria and regrown in a phage-free environment, the newly generated bacteria exhibit phage sensitivity similar to their parental cells. Thus the coexistence of bacteraium and phage is not due to genetic mutation but is intrinsic to nonlinear dynamics of the interacting species. Our measurements showed that the bacterial population is sustained by a small number of persistors that provide ''physiological refuge'' against phage infection. The measured bacterium and phage population dynamics can be reasonably account for by a simple mathematic model that takes into account stochastic switching between normal cells and persister cells.

2225-Plat

Driving DNA Tweezers with an in vitro Transcriptional Oscillator

Eike Friedrichs[1], Jongmin Kim[2], Ralf Jungmann[1], Elisa Franco[2], Richard Murray[2], Erik Winfree[2], Friedrich C. Simmel[1].
[1]Technische Universität München, Garching, Germany, [2]California Institute of Technology, Pasadena, CA, USA.