LATE ABSTRACTS

E. Technological Frontiers

E18. Combining Microfluidics and Microarray for Complex Cell Signaling Study

Zhizhong Yin[1], Sheng-Ce Tao[2] , Raymond Cheong[3], Andre Levchenko[1]
[1]*Department of Biomedical Engineering, Johns Hopkins University,* [2]*High Throughput Biology Center, Johns Hopkins School of Medicine,* [3]*Department of Biomedical Engineering, Johns Hopkins University*
alev@jhu.edu

Cell signaling determines how a cell responds to its environment. Extracellular stimulations are relayed in the cell through pathways. Often, pathway is shared by many stimuli and one stimulus could stimulate many pathways. Here, we present a new platform for complex cell signaling studies in a high-throughput manner by combining microfluidics with protein microarray technologies. Ligands at different concentrations and combinations were spotted on a glass substrate with electrode array and N-hydroxysuccinimide coating. Cells were seeded into a Polydimethylsiloxane (PDMS) chip bonded on the substrate and patterned exactly on the spots by dielectropheretic force. Cells then attach and spread on the spots coming into contact with ligands.

F. Regulatory Systems

F65. A mechanism for regulation of bistability in gene expression

Saurabh Paliwal[1], Pablo A. Iglesias[2], Andre Levchenko[1]
[1]*Department of Biomedical Engineering, The Johns Hopkins University,* [2]*Department of Electrical and Computer Engineering, The Johns Hopkins University*
spaliwal@jhu.edu

In response to external inputs, many cellular biochemical networks display bistable switching, which is often attributed to positive feedback loops. Yeast cells display bimodal gene expression in response to a range of pheromone concentrations, resulting from a combination of bistable gene expression and stochastic noise. MAPK (Fus3 and Kss1) mediated phosphorylation of the mating transcription factor Ste12, followed by up-regulated expression of mating genes results in many positive feedbacks. Additionally, unphosphorylated Kss1-mediated repression of Ste12 contributes to the bistability. In light of this biological example, we have investigated the role of negative transcriptional regulation in modulating bistable responses.

F66. Dynamic modeling of DNA damage and repair processes

Gabriele Lillacci[1], Mustafa Khammash[1]
[1]*Department of Mechanical Engineering, University of California, Santa Barbara*
gabriele@engr.ucsb.edu

DNA damage and repair processes are crucial to the onset and therapy of cancer. A better understanding of their operation and of how to control them could be relevant to the development of new therapeutic approaches. We propose a general deterministic modeling framework for gene expression and then apply it to a genetic network built around the p53 gene, which is responsible of sensing DNA damage. We use the model to analyze the behavior of the network in both healthy and pathological situations, and to study the interaction between the network and a particular class of drugs. We also study the state and parameters estimation problems for this system, and try to solve it by applying an observer based on an hybrid Kalman filter.

F67. Investigating the Systems Properties of the Mammalian DNA-Damage Response

Jared E. Toettcher[1], Alexander Loewer[2], Gerard J. Ostheimer[3], Michael B. Yaffe[3], Galit Lahav[2], Bruce Tidor[1]
[1]*Department of Biological Engineering, Massachusetts Institute of Technology,* [2] *Department of Systems Biology, Harvard Medical School,* [3]*Department of Biology, Massachusetts Institute of Technology*
tidor@mit.edu

The cell cycle consists of the proper sequential processes of DNA replication, chromosome segregation and cytokinesis. After DNA damage, the cell cycle arrests to allow genomic repair by modulating the activities of cyclin/Cdk complexes. We present a model of the DNA damage response and cell cycle arrest. The model differentiates between G2 arrests due to cyclin/Cdk inactivation and transcriptional repression. We fit the model to arrested U2OS cells' cyclin levels; this fit is consistent with arrest by cyclin/Cdk inactivation, not transcriptional repression. Finally we identify arrest conditions from which cells might incorrectly re-enter the cell cycle and endoreduplicate their DNA, and are currently testing this prediction.

G. Systems Bioinformatics: Tools

G43. The Pi Markup Language—Toward Pi-Model Exchange

Dagmar Koehn[1], Mathias John[1]
[1]University of Rostock, Germany
dk103@informatik.uni-rostock.de

For the Pi-calculus, there exist many notations - a fact that hampers model exchange and reuse. We introduce a first approach for the Pi-calculus Markup Language (PiML), a common notation-independent format for validating, storing, and exchanging Pi-models. PiML is a particular XML Schema with full Pi-syntax expressiveness allowing for the transformation of existing Pi-models into PiML representations and vice versa in a consistent manner. The PiML schema supports definitions of actions as well as of nested parallel processes and summations. Models can be queried using a common query language and are comparable through matching techniques. Extensions of the Pi-calculus can be added by designing additional modules.

H. Systems Bioinformatics: Analysis

H58. Automatic Integration of Kinetic Data for Metabolic Network Modeling

Wolfram Liebermeister [1], Jannis Uhlendorf[1], Simon Borger[1], Edda Klipp[1]
[1]*Computational Systems Biology, Max Planck Institute for Mo-*

LATE ABSTRACTS

lecular Genetics, Berlin
klipp@molgen.mpg.de

Dynamic modeling of metabolism often relies on uncertain or contradictory kinetic parameters or data. We developed methods to integrate diverse thermodynamic and kinetic data, keeping track of all uncertainties. We describe model parameters by statistical distributions instead of fixed values. Bayesian estimation allows combining data of different accuracy and with prior assumptions about parameter ranges. The automatic modeling workflow starts from a structural model; a collection of original data is retrieved automatically and a kinetic model with convenience rate law and consistent parameters is constructed. A second Bayesian estimation can integrate dynamic quantities such as measured metabolite or enzyme concentrations and fluxes.

I. Systems Biomedicine

I44. Progression Analysis of Disease

Nagarajan[1], Monica Nicolau[2], Gurjeet Singh[1], Gunnar Carlsson[2]
[1]*Institute for Computational and Mathematical Engineering, Stanford University, Stanford, CA,* [2]*Department of Math, Stanford University, Stanford, CA*
gunnar@math.stanford.edu

Genomic data analysis provides a wealth of information about disease, allowing classifications into distinct disease subtypes. It does not provide information about disease progression: whether a cohort comprises distinct diseases or different developmental stages of one disease is a question that is both difficult and of paramount importance. We introduce a method to infer disease progression from gene expression data. The method relies on a combination of two mathematical methods of analysis: the first (DSGA) identifies the component of data relevant to disease, the second (MAPPER) extracts continuous progression drifts among patients. Our method is able to sort patients correctly according to progressively acute clinical characteristics.

J. Multiscale Networks

J48. Tuned protein variability in yeast metabolism

Gal Chechik[1], Muxing Chen[2], Daphne Koller [2]
[1]*Google Research,* [2]*Stanford University*
gal@ai.stanford.edu

Fluctuations in protein abundance are highly variable across proteins (Newman 2006). While variability could reflect uncontrolled noise, it could also reflect useful flexibility, allowing cells to explore the space of viable protein-level configurations. Here we test the hypothesis that cells allow larger fluctuations for those proteins that can be easily compensated for. We use flux balance analysis in the metabolic network of S. cerevisiae to quantify the cellular cost required to preserve growth under protein fluctuations. We find a significant negative correlation between the protein variability and compensation cost: high cost enzymes have low variability, consistent with the hypothesis of controlled variability.

J49. Dynamics and design principles of a basic regulatory module controlling metabolic pathways

Victor Chubukov[1], Chen-Shan Chin[2], Emmitt R. Jolly[3], Joe Derisi[2], Hao Li[2]
[1]*Joint Graduate Group in Bioengineering, Universirt of California, Berkeley/Univesirt of California, San Francisco,* [2]*Department of Biochemistry, University of California, San Francisco,* [3]*Department of Pathology, University of California, San Francisco*
chubukov@genome.ucsf.edu

By looking at gene induction with high temporal resolution, we have obtained much insight into the transcriptional regulation of a metabolic pathway. Although genes for all the enzymes in the pathway are thought to be regulated by the same transcription factors, we observe drastically different dynamic responses, as well as different responses to genetic perturbations. The contrasting behaviors seem to be related to the intricate link between metabolism and gene expression created by a small-molecule intermediate of the pathway acting as a transcriptional activator. Mathematical modeling correctly predicts responses to new perturbations, and suggests constraints on both timing and level of gene induction imposed by the network architecture.