7.342 Systems Biology: Stochastic Processes and Biological Robustness

Fall 2008, Thursdays 1 -3 pm, Room 68-151
(NOTE: The time is flexible and subject to change according to the needs of the students).

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Course Description

Molecular biology has been extremely successful in deciphering the details of specific cellular biochemical interactions, such as those that control inter- and intracellular signaling and gene expression. However, a full understanding of cellular function will require an understanding of how all of these interactions work together in a network to perform particular tasks. Such an understanding is the goal of the new field of systems biology. In this seminar, we will discuss some of the main themes that have arisen in this field, including the concepts of robustness, stochastic cell-to-cell variability and the evolution of molecular interactions within complex networks. Robustness is a property of many natural biological networks whereby the behavior of the network is insensitive to variations in the numbers of inputs and the strengths of interactions. One classic example is bacterial chemotaxis, in which the bacterial food sensing mechanism is insensitive to perturbations in the levels of key proteins. This insensitivity to variations is particularly important given recent work demonstrating that gene expression has a strongly random component, leading to large variations from cell to cell even in genetically identical populations. In certain networks, this "gene expression noise" can lead to intrinsically random divergence in developmental fates. We will also discuss networks in a more global context, considering the structure and evolutionary dynamics of networks in whole organisms. Finally, we will study how researchers in the field of synthetic biology are using such new knowledge about biological networks to create artificial gene networks capable of performing new functions. Examples range from simple genetic switches and oscillators to the transplantation of entire networks capable of producing drugs, biofuels, and synthetic materials.

Course Objectives:

The main objectives of this course are to introduce students to the primary scientific literature and the process of finding/reading research papers and to expose students to the new field of systems biology. In the process of reading the assigned publications, you will learn how to analyze papers to extract key points and to examine scientific papers critically. Our focus will be on papers that have made significant conceptual contributions to systems biology. We will discuss experimental methodology and the principles of experimental design, control experiments and the interpretation of experimental data. We also aim to introduce students to the theoretical aspects of

biology. While some mathematical background will be helpful in this regard, it is not required. Part of our goal is to expose those with little theoretical background to some of the interesting theories that have helped to make systems biology a remarkably interdisciplinary field.

Requirements
Grading: P/F, 6 units, no listeners

Prerequisites
The prerequisite for this course is 7.01X. Also helpful would be 18.03, 7.03, 7.05, 7.06, or 7.28. Depending upon the interests of the students we may emphasize more or less of the mathematical aspects of this subject.

Assignments
For each of the two written assignments we will distribute the abstract of a published paper. In two pages (double-spaced) or less, please describe the experiments (including controls) that might have been done to justify the abstract.
Paper #1, due October 16, 2008
Paper #2, due November 20, 2008

Schedule

Note: we are considering including a field trip to a systems biology lab in the Cambridge area during the class. The specifics of the trip have yet to be determined.

Day 1, September 4, 2008: Introduction to the class and topic.
The instructors and students will introduce themselves. The instructors will discuss the administrative aspects of the course and present a general overview of systems biology and in particular the aspects that will be the focus of the course. This summary is the only lecture that will be given in the course, and we hope nonetheless for an interactive environment during the first day.

Day 2, September 11, 2008: Simple synthetic networks
Much of the recent interest in systems biology has been motivated by the need to understand how simple artificially constructed genetic networks operate in the cell. Early efforts included the production of simple networks capable of producing genetic oscillators and toggle switches. This week we will discuss two examples of artificial networks that led to many of the recent attempts at understanding network function and the consequences of gene expression variability.

- "A synthetic oscillatory network of transcriptional regulators"
  MB Elowitz and S Leibler
  Nature **403**, 335 – 338 (2000)
- "Positive feedback in eukaryotic gene networks: cell differentiation by graded to binary response conversion"
  A Becskei, B Séraphin, L Serrano
  The EMBO Journal **20**, 2528 – 2535 (2001)

Day 3, September 18, 2008: Noise in gene expression (I)
One of the first findings in systems biology was that gene expression is a fundamentally stochastic phenomenon. In particular, it appears that the randomness inherent to the biochemical processes involved in gene expression can lead to significant cell-to-cell variability in the numbers of proteins and mRNAs, leading to "non-genetic individuality" among genetically identical organisms. This week, we discuss a classic study of variability in bacterial gene expression and introduce the concepts of extrinsic and intrinsic noise. We also will read a paper that discusses some of the theoretical underpinnings of stochastic chemical kinetics and present concepts that have been widely applied to stochastic gene expression.

- "Stochastic gene expression in a single cell"
  MB Elowitz, AJ Levine, ED Siggia, and PS Swain
  Science **297**, 1183 – 1186 (2002)
- "Exact stochastic simulation of coupled chemical reactions"
  DT Gillespie
  The Journal of Physical Chemistry **81**, 2340 – 2361 (1977)

Day 4, September 25, 2008: Noise in gene expression (II)
Lately, a number of studies have indicated that stochastic gene expression in eukaryotic cells can result in even greater variability than that observed in bacteria. This variation is thought to happen because transcription in these organisms occurs in bursts rather than at a steady rate, leading to very broad population distributions of mRNAs and proteins. This week we will discuss two papers that examine stochastic gene expression in eukaryotes. One is a classic study of variability in cultured cells, and another is a study that utilizes quantitative PCR-based methods to count mRNAs in individual cells.

- "Gene expression profiling in single cells from the pancreatic islets of Langerhans reveals lognormal distribution of mRNA levels"
  M Bengtsson, A Stahlberg, P Rorsman, M Kubista
  Genome Research **15**, 1388 – 1392 (2005)
- "The dose dependence of glucocorticoid-inducible gene expression results from changes in the number of transcriptionally active templates"
  MS Ko, H Nakauchi, N Takahashi
  The EMBO Journal **9**, 2835 – 2842 (1990)

Day 5, October 2, 2008: Noise in gene expression (III)
Now that stochastic gene expression has been established as being an important biological effect, researchers are delving ever more deeply into the process of gene expression itself. This analysis includes trying to understand what biochemical reactions are the most prone to stochastic behavior and thus contribute the most to cellular variability. This week's papers include a theoretical examination of the sources of stochastic gene expression as well as a remarkable real-time visualization of stochastic gene expression.

- "Stochastic mechanisms in gene expression"
  HH McAdams and AP Arkin
  Proceedings of the National Academy of Sciences **94**, 814 – 819 (1997)

- "Probing gene expression in live cells, one protein molecule at a time"
  J Yu, J Xiao, X Ren, K Lao, XS Xie
  Science **311**, 1600 - 1603 (2006)

Day 6, October 9, 2008: Structure of biological networks
One of the central goals of systems biology is to understand how the wiring of genetic networks allows them to perform cellular functions. While much is now known about what sets of genes interact, only recently have we begun to understand why those particular sets of interactions are useful. Through this week's papers, we will learn about efforts to find functional units ("network motifs") within large gene interaction networks and also check whether a particularly common motif actually work as theory predicts.

- "Negative Autoregulation Speeds the Response Times of Transcription Networks"
  N Rosenfeld, MB Elowitz, U Alon
  Journal of Molecular Biology **323**, 785 – 793 (2002)
- "Network motifs in the transcriptional regulation network of Escherichia coli"
  SS Shen-Orr, R Milo, S Mangan, U Alon
  Nature Genetics **31**, 64 - 68 (2002)

Day 7, October 16, 2008: Network evolution and adaptation
Paper #1 is due today
We often discuss genetic networks from a functional standpoint, but we must always remember that these networks exist in the context of evolutionary challenges and constraints. In this week's papers we will see two very different responses to novel environmental challenges.

- "Optimality and evolutionary tuning of the expression level of a protein"
  E Dekel and U Alon
  Nature **436**, 588 – 592 (2006)
- "Genome-wide transcriptional plasticity underlies cellular adaptation to novel challenge"
  S Stern, T Dror, E Stolovicki, N Brenner, E Braun
  Molecular Systems Biology **3**, 1 – 9 (2007)

Day 8, October 23, 2008: Chemotaxis I
Microorganisms live in an environment very different from the world that we are used to. This week we will discuss a paper describing the basic physical challenges facing a cell. Although physics in the regime of small size and high viscosity make some things impossible, microbes have nevertheless found some surprising solutions to the challenges they face.

- "Life at low Reynolds number"
  EM Purcell
  American Journal of Physics **45**, 3 – 11 (1977)
- "Physics of chemoreception"
  HC Berg and EM Purcell
  Biophysical Journal **20**, 193 – 219 (1977)

Day 9, October 30, 2008: Chemotaxis II

This week we discuss two papers that probe the ability of *E. coli* to swim towards food sources. For several decades it has been known that this chemotaxis occurs by alternating "runs," in which the cell swims straight, followed by "tumbles," in which the orientation of the cell is randomized. The cell is able to move towards food sources by altering the frequency of these tumbles depending upon whether things are improving or getting worse. This week's papers show that because the steady-state frequency of tumbling is independent of the concentration of food sources (robustness), the cell is able to respond to gradients over a wide range of concentrations.

- "Robustness in bacterial chemotaxis"
  U Alon, MG Surette, N Barkai, S Leibler
  Nature **397**, 168 – 170 (1999)
- "Receptor sensitivity in bacterial chemotaxis"
  V Sourjik and HC Berg
  Proceedings of the National Academy of Sciences **99**, 123 – 127 (1997)

Day 10, November 6, 2008: Circadian Oscillations

Circadian oscillations are 24-hour cellular oscillations that can be entrained by the day-night cycle—they are responsible for many phenomena, including, for instance, jet lag. This week, we discuss a paper that examines the circadian clock in cyanobacteria and another paper about the very different circadian clock used by mammals.

- "Ordered phosphorylation governs oscillation of a three-protein circadian clock"
  MJ Rust, JS Markson, WS Lane, DS Fisher, EK O'Shea
  Science **318**, 809 - 812 (2007)
- "Circadian gene expression in individual fibroblasts cell-autonomous and self-sustained oscillators pass time to daughter cells"
  E Nagoshi, C Saini, C Bauer, T Laroche, F Naef, U Schibler
  Cell **119** , 693 - 705 (2004)

Day 11, November 13, 2008: Field trip

This week, we will take a field trip to a local systems biology lab (lab to be determined). The goal is to expose students to current work in the field while also highlighting some of experimental methods that systems biologists use in their research.

Day 12, November 20, 2008: Noise in development

Paper #2 is due today

The developmental of an organism from a single cell to an adult is one of the most complex biological programs in existence. Yet, despite its complexity, the program usually executes with remarkable fidelity, a prime example of biological robustness. However, there are a few important instances where variability, arising from stochastic gene expression or otherwise, can lead the program to alternate endings. This week, we explore one paper in which stochastic gene expression is used by an organism to produce useful variability in development and another paper in which a different mechanism leads to randomly determined cell fates in *C. elegans*.

- "Stochastic spineless expression creates the retinal mosaic for colour vision", MF Wernet, EO Mazzoni, A Celik, DM Duncan, I Duncan, C Desplan

Nature **440**, 174 – 180 (2006)

- "Post-transcriptional regulation of the E/Daughterless ortholog HLH-2, negative feedback, and birth order bias during the AC/VU decision in *C. elegans*"
  X Karp and I Greenwald
  Genes and Development **17**, 3100 – 3111 (2003)

Day 13, December 4, 2008: Synthetic biology

At the beginning of this course we read several papers in which very simple genetic networks were constructed. These projects allowed experimentalists to test models of gene expression and also provided a step towards engineering entirely new cellular functions. In our last week we will discuss two short papers describing the increasingly ambitious efforts of synthetic biologists to bend nature to man's will.

- "Synthetic biology: engineering *E. coli* to see light"
  A Levskaya, AA Chevalier, JJ Tabor, ZB simpson, LA Lavery, M Levy , EA Davidson, AScouras, AD Ellington, EM Marcotte, CA Voigt
  Nature **438**, 441-2 (2005)
- "Genome transplantation in bacteria: changing one species to another"
  C Lartigue, JI Glass, N Alperovich, R Pieper, PP Parmar, CA Hutchison, III, HO Smith, JC Venter
  Science **317**, 632 - 638 (2007)