Systems Biology

‘modeling biological networks’

Introducing ...

Lectures: TR 1:00 -2:30 PM
Rm. 6-120

Recitations: W 4:00 - 5:00 PM
Rm. 26-204
(under construction)

Alexander van Oudenaarden
Rm. 68-371B
avano@mit.edu

Jialing Li
jialing3@gmail.com
Rm. 68-383

Bernardo Pando
bpando@mit.edu
Rm. 68-365

Take-home Exams:

<table>
<thead>
<tr>
<th>Exam</th>
<th>Due Date</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Exam 1</td>
<td>10/06/09</td>
<td>15%</td>
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<tr>
<td>Exam 2</td>
<td>10/20/09</td>
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<td>Exam 3</td>
<td>11/03/09</td>
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<td>Exam 4</td>
<td>11/17/09</td>
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<td>Exam 5</td>
<td>12/01/09</td>
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<tr>
<td>Final</td>
<td>12/10/09</td>
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Final Problem Set will be a take-home PS broadly covering the course material

Text books: none

Handouts will be available on-line

Good reference (biology textbook):
Molecular biology of the cell
Alberts et al.

Matlab will be used intensively during the course, make sure you known (or learn) how to use it (necessary for problem sets)

Web-page: web.mit.edu/biophysics/sbio
(contains all course materials)
Intrinsic challenge of this class:

mixed audience with wildly different backgrounds

⇒ read up on your biology or math if needed

⇒ recitations (W 4PM, Rm. 26-204) are intended to close the gaps and prepare for homework

Systems Biology

GOAL: develop a quantitative (mathematical) understanding of the biological function of genetic and biochemical networks

Three levels of complexity

I Systems Microbiology (~14 Lectures)

‘The cell as a well-stirred biochemical reactor’

II Systems Cell Biology (~8 Lectures)

‘The cell as a compartmentalized system with concentration gradients’

III Systems Developmental Biology (~3 Lectures)

‘The cell in a social context communicating with neighboring cells’
Introduction phage biology

Phage genome:
48512 base pairs ~ 12 kB
'phage.jpg' ~ 10 kB

Excellent book:
A genetic switch by Mark Ptashne
The central dogma defines three major groups of biomolecules (biopolymers):

1. DNA (passive library, $6 \times 10^9$ bp, 2 m/cell, 75$\times 10^{12}$ cells/human, total length $150\times 10^{12}$ m/human ~ 1000 rsun-earth)
2. RNA (‘passive’ intermediate)
3. Proteins (active work horses)
4. Small molecules (sugars, hormones, vitamins, ‘substrates’ etc.)

The lysis-lysogeny decision:

As the phage genome is injected, phage genes are transcribed and translated by using the host’s machinery. Which set of phage proteins are expressed determines the fate of the phage: lysis or lysogeny.

The lysis-lysogeny decision is a genetic switch

Single repressor dimer bound - three cases:

1. Negative control, dimer binding to OR2 inhibits RNAp binding to right $P_R$ promoter.
2. Positive control, dimer binding to OR2 enhances RNAp binding to left $P_{RM}$ promoter.

only ‘space’ for one RNA polymerase (mutual exclusion)

more repressor monomers

more repressor dimers
II Negative control, dimer binding to OR1 inhibits RNAp binding to right $P_R$ promoter.

Negative control, dimer binding to OR1 inhibits RNAp binding to left $P_{RM}$ promoter (too distant).

III Negative control, dimer binding to OR3 inhibits RNAp binding to left $P_{RM}$ promoter.

Positive control, dimer binding to OR3 allows RNAp binding to right $P_R$ promoter.

Repressor-DNA binding is highly cooperative

Intrinsic association constants:

$K_{OR1} \sim 10\ K_{OR2} \sim 10\ K_{OR3}$

However $K_{OR2}^* \gg K_{OR2}$ (positive cooperativity)

Flipping the switch by UV:

In lysogenic state, [repressor] is maintained at constant level by negative feedback ("chemo-stat")
UV radiation induces SOS response (DNA damage)
protein RecA becomes specific protease for λ repressor

after cleavage monomers cannot dimerize anymore,
[repressor dimers] decreases,
when all repressors vacate DNA, Cro gene switches on.

Cooperative effects make sharp switch
(‘well defined’ decision)

Note: several layers of cooperativity:
dimerization, cooperative repressor binding

Stochastic Gene Expression
in a Lentiviral Positive-Feedback Loop:
HIV-1 Tat Fluctuations Drive Phenotypic Diversity
‘The cell as a well-stirred biochemical reactor’

L1 Introduction
L2-3 Chemical kinetics, Equilibrium binding, cooperativity
L4 Lambda phage
L5 Cellular memory
L6-7 Genetic switches
L8-9 *E. coli* chemotaxis
L10 Stability analysis
L11-12 Genetic oscillators
L13-14 Stochastic chemical kinetics

The Flagellum

Absence of chemical attractant
Presence of chemical attractant

chemical gradient sensed in a temporal manner

Chemotaxis of *Escherichia coli*

CW rotation: ‘tumbles’
CCW rotation: ‘runs’

absence aspartate gradient → random walk (diffusion)
presence aspartate gradient → biased random walk towards aspartate source

Chemotactic pathway in *E. coli*. 

30
Adaptation:

Correlation of receptor methylation with behavioral response.

What is the simplest mathematical model that is consistent with the biology and reproduces the experiments?

I Systems Microbiology (14 Lectures)

‘The cell as a well-stirred biochemical reactor’

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Common Elements in the Design of Circadian Oscillators

Positive element(s)

Negative element(s)

clock gene(s)

output - clock controlled genes

rhythmic metabolism and behavior

Positive elements in circadian loops:
- kaiA in Synechococcus
- WHITE COLLAR-1 & WC-2 in Neurospora
- CLK & CYC in Drosophila
- CLOCK & BMAL1 (MOP3) in mammals

Negative elements in circadian loops:
- kaiC in Synechococcus
- FREQUENCY in Neurospora
- PERIOD and TIMELESS in Drosophila
- PER1, PER2, PER3 (& TIMELESS?) in mammals
The circadian clock consists of only 3 proteins: KaiA, KaiB and KaiC.
The circadian clock consists of only 3 proteins and can be reconstituted in vitro

Modeling the cell cycle
II Systems Cell Biology (8 Lectures)

‘The cell as a compartmentalized system with concentration gradients’

- L15 Diffusion, Fick’s equations, boundary and initial conditions
- L16 Local excitation, global inhibition theory
- L17-18 Models for eukaryotic gradient sensing
- L19-20 Center finding algorithms
- L21-22 Modeling cytoskeleton dynamics

http://www.mpf.biol.vt.edu/research/budding_yeast_model

Eukaryotic Chemotaxis

How is this different from E. coli chemotaxis?

temporal versus spatial sensing
cyclic AMP (cAMP) is an attractant for Dictyostelium (social amoeba)

Response of Dictyostelium to cAMP

- Uniform step in cAMP
- cAMP gradient

Initial distribution:
- $t = 3 \, s$

Steady-state distribution:
- $t < 3 \, \infty$

Uniform and transient

Polarized and persistent
Response of Dictyostelium to pulsed cAMP

geometry of cell: circular
inside cytoplasm: well-stirred
inside membrane: diffusion-limited

GFP-PH binds special lipids in membrane:
PIP2 and PIP3

The molecules in the model:

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how to find the middle of a cell?

Most of MinE accumulates at the rim of this tube, in the shape of a ring (the E ring). The rim of the MinC/D tube and associated E ring move from a central position to the cell pole until both the tube and ring vanish. Meanwhile, a new MinC/D tube and associated E ring form in the opposite cell half, and the process repeats, resulting in a pole-to-pole oscillation cycle of the division inhibitor. A full cycle takes about 50 s.
Recent results demonstrate that the min proteins assemble in helices.
II Systems Cell Biology (8 Lectures)

‘The cell as a compartmentalized system with concentration gradients’

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L21-22 Modeling cytoskeleton dynamics

Center finding in an eukaryotic cell: fission yeast
The importance of the cytoskeleton

Chang et al.
kinesin is a molecular motor that runs to the plus end of a MT

dynein is a molecular motor that runs to the minus end of a MT
Black tetra

Movies!

III Systems Developmental Biology (3 Lectures)

‘The cell in a social context communicating with neighboring cells’

L23  Quorum sensing
L24-25 Drosophila development
major advantage of Drosophila:
each stripe in the embryo corresponds to certain body parts in adult fly

zygote (contains DNA from father and mother, zygotic effects)

egg (contains maternal components, maternal effects, only determined by mother)

nuclei form plasma membrane

early development
radioactive labeled RNA reveals localization at pole

interpreting the bicoid gradient (created by maternal effects) by zygotic effect (gene expression by embryo itself)

hunchback is a zygotic effect!

hunchback reads the bicoid gradient
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