Systems Biology

'modeling biological networks'

Introducing...

Lectures:
TR 1:00 -2:30 PM
Rm. 6-120
Alexander van Oudenaarden
Rm. 13-2008
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Recitations:
W 4:00 - 5:00 PM
Rm. 26-302
Bernardo Pando
Rm. 13-2042
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Take-home Exams:

Exam 1    due 10/05/05   15 %
Exam 2    due 10/20/05   15 %
Exam 3    due 11/03/05   15 %
Exam 4    due 11/15/05   15 %
Exam 5    due 11/29/05   15 %
Final     due 12/13/05   25 %

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. 8-302) are intended to close the gaps and prepare for homework

Systems Biology ≈ Network Biology

**GOAL:** develop a quantitative understanding of the biological function of genetic and biochemical networks

- function of gene product A-F can be known in detail but this is not sufficient to reveal the biological function of the INPUT-OUTPUT relation
- a system approach (looking beyond one gene/protein) is necessary to reveal the biological function of this whole network
- what is the function of the individual interactions (feedbacks and feedforwards) in the context of the entire network?

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)

The fourth (and final) group consists of so-called ‘small molecules’.

4. Small molecules (sugars, hormones, vitamins, ‘substrates’ etc.)

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**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.

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**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.

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

Cl OFF Cl ON Cl OFF

Cro OFF Cro OFF Cro OFF

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.
I Systems Microbiology (14 Lectures)

‘The cell as a well-stirred biochemical reactor’

L1 Introduction
L2 Chemical kinetics, Equilibrium binding, cooperativity
L3 Lambda phage
L4 Stability analysis
L5-6 Genetic switches
L7 *E. coli* chemotaxis
L8 Fine-tuned versus robust models
L9 Receptor clustering
L10-11 Stochastic chemical kinetics
L12-13 Genetic oscillators
L14 Circadian rhythms

The Flagellum

Absence of chemical attractant
Presence of chemical attractant

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
Correlation of receptor methylation with behavioral response.

What is the simplest mathematical model that is consistent with the biology and reproduces the experiments?
**Circadian Oscillations in Single Cells**

![Graph showing bioluminescence over time for different conditions.](image)

**Fig. 3.** Circadian rhythm of bioluminescence in continuous light conditions. The transformed strain AMI34 was cultured at 30°C under a 12 hr/12 hr LD cycle (46 pulses “+” with constant shaking (180 rpm) and then transferred to vials for measurement of bioluminescence. The two traces are from cultures that were previously entrained to LD cycles which were 24 hr out of phase. The last LD cycles preceding LL are illustrated on the abscissa (open bar, light period; filled bar, dark period).

**Fig. 5.** Temperature compensation of the period. Experimental procedures were the same as in Fig. 3, except that the bioluminescence monitored at three temperatures is shown. (a) Rhythm of bioluminescence. (b) Period of the rhythm vs. temperature (bars indicate standard deviation of three or four replicates).
Modeling the cell cycle

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

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Eukaryotic Chemotaxis

How is this different from E. coli chemotaxis?

temporal versus spatial sensing

cyclic AMP (cAMP) is an attractant for Dictyostelium (social amoeba)
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Response of Dictyostelium to cAMP

- **uniform step in cAMP**
  - initial distribution $t \sim 3\ s$
  - steady-state distribution $t \to \infty$
- **cAMP gradient**
  - uniform and transient
  - polarized and persistent

Response of Dictyostelium to pulsed cAMP
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The molecules in the model:

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

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.

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

III Systems Developmental Biology (3 Lectures)
‘The cell in a social context communicating with neighboring cells’

L23 Quorum sensing
L24-25 Drosophila development
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
egg (contains maternal components, maternal effects, only determined by mother)

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

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

Houchmandzadeh et al.

Center finding in the Drosophila embryo

bicoid

hunchback