## I Systems Microbiology (13 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
- L7-9 E. coli chemotaxis
- L10-11 Genetic oscillators
- L12-13 Stochastic chemical kinetics

## II Systems Cell Biology (9 Lectures)

*The cell as a compartmentalized system with concentration gradients*

- L15 Diffusion, Fick's equations, boundary and initial conditions
- L16-17 Local excitation, global inhibition theory
- L18-19 Models for eukaryotic gradient sensing
- L20-21 Center finding algorithms
- L22-23 Modeling cytoskeleton dynamics

## III Systems Developmental Biology (2 Lectures)

*The cell in a social context communicating with neighboring cells*

- L23 Quorum sensing
- L25 Drosophila development
Main take home messages from this course:

1. translate the biology into a quantitative model:
   given the biology set up the coupled differential equations that capture the essence of the biological phenomena
   (not trivial since 4 papers came up with a different model given the same biological phenomenon, which assumptions to make is critical)

2. analysis of the system of differential equations
   stability analysis (both in space and time)

3. interpretation of the mathematical analysis, what are the biological conclusions?
   e.g. if the imaginary part of the eigenvalue is non-zero, what does this mean for the underlying biology?

4. develop a taste for the potential of these systems
   approaches for biological problems that you may encounter in the future

Developmental Systems Biology

‘Building an organism starting from a single cell’

Introducing: Drosophila melanogaster
(or the fruitfly)

Great book: ‘The making of the fly’ by Peter Lawrence

Model Organisms for Biomedical Research

Mammalian Models:
- Mouse
- Rat

Non-Mammalian Models:
- S. cerevisiae (budding yeast)
- D. discoideum (social amoebae)
- C. elegans (round worm)
- D. melanogaster (fruit fly)
- D. rerio (zebrafish)
- Xenopus (frog)

We hope this website provides you with information about national and international activities and major resources that are being developed to facilitate biomedical research using the animal models listed here. For organisms not listed, web pages may be developed in the future.

If you have suggestions as to how we can enhance the information provided, please send a message to Betty Graham at bettie.gram@mshri.org.
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, RNA, proteins)

Pioneering experiments by Klaus Sander (1958) on leaf-hoppers

disrupted stripes

Pioneering experiments by Klaus Sander (1958)
on leaf-hoppers

nuclei form plasma membrane

Early development

MOVIE!
http://flymove.uni-muenster.de
ligation and transplantation experiments indicate the presence of morphogens created/destroyed at the poles of the embryo

First morphogen: bicoid (true maternal)
transplantation of bicoid can rescue cells
head fold shift to right for increasing number of gene copies in mother

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

a lot of zygotic gene controls formation of stripes

recent experimental paper explores relation between bicoid and hunchback quantitatively:

only gene that makes hb more noisy is Staufen

How can you make a steep step in hunchback exactly in the middle of the embryo from a noisy bicoid gradient?

Nobody knows ...

Second example:

Robustness of Drosophila patterning
remember robustness of chemotaxis (L9-10):

explore robustness in Drosophila patterning

main molecules of interest:
Scw: BMP (bone morphogenetic protein) ligand
Sog: a BMP inhibitor
Tld: protease (cleaves Sog)
29 perivitelline fluid activates next step in development

30 simple reaction-diffusion model:

\[
\frac{\partial [\text{Sog}]}{\partial t} = D_s \frac{\partial^2 [\text{Sog}]}{\partial x^2} - k_h [\text{Sog}][\text{Scw}] + k_s [\text{Sog} - \text{Scw}] - \alpha [\text{Tld}][\text{Sog}]
\]

\[
\frac{\partial [\text{Scw}]}{\partial t} = D_{\text{scw}} \frac{\partial^2 [\text{Scw}]}{\partial x^2} - k_h [\text{Sog}][\text{Scw}] + k_s [\text{Sog} - \text{Scw}] + \lambda [\text{Tld}][\text{Sog} - \text{Scw}]
\]

\[
\frac{\partial [\text{Sog} - \text{Scw}]}{\partial t} = D_c \frac{\partial^2 [\text{Sog} - \text{Scw}]}{\partial x^2} + k_s [\text{Sog}][\text{Scw}] - k_s [\text{Sog} - \text{Scw}] - \lambda [\text{Tld}][\text{Sog} - \text{Scw}]
\]

what does this mean?

31 robustness analysis

32 why robust, ideal model: \(D_{\text{BMP}}=0\), \(\alpha=0\), \(k_b=0\)

\[
0 = D_s \frac{\partial^2 [\text{Sog}]}{\partial x^2} - k_h [\text{Sog}][\text{Scw}]
\]

\[
0 = 0 - k_s [\text{Sog}][\text{Scw}] + \lambda [\text{Tld}][\text{Sog} - \text{Scw}]
\]

\[
0 = D_c \frac{\partial^2 [\text{Sog} - \text{Scw}]}{\partial x^2} + k_s [\text{Sog}][\text{Scw}] - \lambda [\text{Tld}][\text{Sog} - \text{Scw}]
\]

\[
0 = D_s \frac{\partial^2 [\text{Sog}]}{\partial x^2} - \frac{1}{D_s} \frac{\partial^2}{\partial x^2} [\text{Scw}] = \frac{k_b}{D_s}
\]

Conclusion: power \(n=2\), \(D_{\text{BMP}}<<D_{\text{BMP-Sog}}, \alpha/\lambda<<1\)
THE END