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
‘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
major advantage of Drosphila:

each stripe in the embryo corresponds to certain body parts in adult fly
MOVIE!

http://flymove.uni-muenster.de

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

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

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hunchback reads the bicoid gradient
recent experimental paper explores relation between bicoid and hunchback quantitatively:


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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):

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explore robustness in Drosophila patterning

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main molecules of interest:

Scw: BMP (bone morphogenic protein) ligand

Sog: a BMP inhibitor

Tld: protease (cleaves Sog)
simple reaction-diffusion model:

\[
\frac{\partial[Sog]}{\partial t} = D_s \frac{\partial^2 [Sog]}{\partial x^2} - k_b [Sog][Scw] + k_{-b} [Sog - Scw] - \alpha[Tld][Sog]
\]

\[
\frac{\partial[Scw]}{\partial t} = D_{BMP} \frac{\partial^2 [Scw]}{\partial x^2} - k_b [Sog][Scw] + k_{-b} [Sog - Scw] + \lambda[Tld][Sog - Scw]
\]

\[
\frac{\partial[Sog - Scw]}{\partial t} = D_c \frac{\partial^2 [Sog - Scw]}{\partial x^2} + k_b [Sog][Scw] - k_{-b} [Sog - Scw] - \lambda[Tld][Sog - Scw]
\]

what does this mean?
robustness analysis

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\[
\frac{\partial [Sog]}{\partial t} = D_S \frac{\partial^2 [Sog]}{\partial x^2} - k_b [Sog][Scw] + k_{-b} [Sog - Scw] - \alpha [Tld][Sog]
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\]
\[
\frac{\partial [Sog - Scw]}{\partial t} = D_c \frac{\partial^2 [Sog - Scw]}{\partial x^2} + k_b [Sog][Scw] - k_{-b} [Sog - Scw] - \lambda [Tld][Sog - Scw]
\]

why robust, ideal model: \( D_{BMP} = 0, \alpha = 0, k_{-b} = 0 \)

\[
0 = D_S \frac{\partial^2 [Sog]}{\partial x^2} - k_b [Sog][Scw]
\]
\[
0 = 0 - k_b [Sog][Scw] + \lambda [Tld][Sog - Scw] \quad \rightarrow \quad \frac{\partial^2}{\partial x^2} \frac{1}{[Scw]} = \frac{k_b}{D_S}
\]
\[
0 = D_c \frac{\partial^2 [Sog - Scw]}{\partial x^2} + k_b [Sog][Scw] - \lambda [Tld][Sog - Scw]
\]