Introduction to Mathematical Physiology
I - Biochemical Reactions

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The Dilemma of Modern Biology

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- The parts list is nearly complete. How the parts work together to determine function is essentially unknown.
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How can mathematics help?

- The search for general principles; organizing and describing the data in more comprehensible ways.
- The search for emergent properties; identifying features of a collection of components that is not a feature of the individual components that make up the collection.
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- to divide -
A few words about words

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• to **divide** - find the ratio of two numbers (Mathematician)
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Examples:

- to divide - replicate the contents of a cell and split into two (Biologist)
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- to differentiate -
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• to differentiate - find the slope of a function (Mathematician)
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- a **PDE** - Phosphodiesterase (Biologist)
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- a PDE - Phosphodiesterase (Biologist)

And so it goes with words like germs and fiber bundles (topologist or microbiologist), cells (numerical analyst or physiologist), complex (analysts or molecular biologists), domains (functional analysts or biochemists), and rings (algebraists or protein structure chemists).
Quick Overview of Biology

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  - Time scales: protein conformational changes $\rightarrow$ protein folding $\rightarrow$ action potentials $\rightarrow$ hormone secretion $\rightarrow$ protein translation $\rightarrow$ cell cycle $\rightarrow$ circadian rhythms $\rightarrow$ human disease processes $\rightarrow$ population changes $\rightarrow$ evolutionary scale adaptation
Kinds of Math I Have Used

- Discrete Math - graph theory, finite state automata, combinatorics
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What about Galois Theory? – p.5/28
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- Topology - knots and scrolls, topological invariants
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- Topology - knots and scrolls, topological invariants
- Algebraic Geometry, Projective geometry
Some Biological Challenges

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- Populations and ecosystems - biodiversity, extinction, invasions
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- Imaging and Visualization (Medical imaging, protein structure, etc.)
Resources for Undergraduates

- Edelstein-Keshet (1988)
- Segel (1984)
- Mackey & Glass (1988)
- Ellner & Guckenheimer (2006)
- Hoppensteadt & Peskin (1992)
- Fall, Marland, Wagner, & Tyson (2002)
- Keener & Sneyd (1998)
Biology is characterized by change. A major goal of modeling is to quantify how things change.

Fundamental Conservation Law:

\[ \frac{d}{dt} (\text{stuff in } \Omega) = \text{rate of transport} + \text{rate of production} \]

In math-speak:

\[ \frac{d}{dt} \int_{\Omega} u dV = \int_{\partial \Omega} J \cdot n ds + \int_{\Omega} f dv \]

where \( u \) is the density of the measured quantity, \( J \) is the flux of \( u \) across the boundary of \( \Omega \), \( f \) is the production rate density, and \( \Omega \) is the domain under consideration (a cell, a room, a city, etc.).

Remark: Most of the work is determining \( J \) and \( f \)!
Basic Chemical Reactions

\[ A \xrightarrow{k} B \]

then

\[ \frac{da}{dt} = -ka = -\frac{db}{dt}. \]

With back reactions,

\[ A \xleftrightarrow{k} B \]

then

\[ \frac{da}{dt} = -k_+ a + k_- b = -\frac{db}{dt}. \]

At steady state,

\[ a = a_0 \frac{k_-}{k_- + k_+}. \]
Bimolecular Chemical Reactions

A + C $\xrightarrow{k} B$

then

$$\frac{da}{dt} = -kca = -\frac{db}{dt}$$

(the "law" of mass action).

With back reactions,

$$A + C \xleftarrow{} B$$

$$\frac{da}{dt} = -k_+ca + k_-b = -\frac{db}{dt}.$$ 

In steady state, $-k_+ca + k_-b = 0$ and $a + b = a_0$, so that

$$a = \frac{k_-a_0}{k_+c + k_-} = \frac{K_{eq}a_0}{K_{eq} + c}.$$ 

Remark: $c$ can be viewed as controlling the amount of $a$. 

Why is Math Biology so hard? – p.11/28
Example: Oxygen and Carbon Dioxide Transport

Problem: If oxygen and carbon dioxide move into and out of the blood by diffusion, their concentrations cannot be very high (and no large organisms could exist.)

\[ \text{Problem solved: Chemical reactions that help enormously:} \]

\[ \text{CO}_2 \text{ + H}_2 \text{O} \rightarrow \text{HCO}_3^- + 2\text{H}^+ + 2\text{O}_2 \]

Hydrogen competes with oxygen for hemoglobin binding.

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\[ CO_2 (+H_2O) \overset{\rightleftharpoons}{\underset{\text{in Lungs}}{\text{In Tissue}}} HCO_3^- + H^- \]

\[ Hb + 4O_2 \overset{\rightleftharpoons}{\underset{\text{in Lungs}}{\text{In Tissue}}} Hb(O_2)^4 \]
Example: Oxygen and Carbon Dioxide Transport

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\begin{align*}
CO_2 & \leftrightarrow HCO_3^- + H^- \\
Hb + 4O_2 & \leftrightarrow Hb(O_2)_4
\end{align*}
\]

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Hydrogen competes with oxygen for hemoglobin binding.
Example II: Polymerization

\[ A_n + A_1 \leftrightarrow A_{n+1} \]

\[ \frac{da_n}{dt} = k_- a_{n+1} - k_+ a_n a_1 - k_- a_n + k_+ a_{n-1} a_1 \]

Question: If the total amount of monomer is fixed, what is the steady state distribution of polymer lengths?

Remark: Regulation of polymerization and depolymerization is fundamental to many cell processes such as cell division, cell motility, etc.
Enzyme Kinetics

\[ S + E \xrightleftharpoons{\kappa_2} C \xrightarrow{\kappa_2} P + E \]

\[
\frac{ds}{dt} = k_- c - k_+ se \\
\frac{de}{dt} = k_- c - k_+ se + k_2 c = -\frac{dc}{dt} \\
\frac{dp}{dt} = k_2 c
\]

Use that \( e + c = e_0 \), so that

\[
\frac{ds}{dt} = k_-(e_0 - e) - k_+ se \\
\frac{de}{dt} = -k_+ se + (k_- + k_2)(e_0 - e)
\]

Why is Math Biology so hard? – p.14/28
The QSS Approximation

Assume that the equation for $e$ is "fast", and so in quasi-equilibrium. Then,

$$(k_- + k_2)(e_0 - e) - k_+se = 0$$

or

$$e = \frac{(k_- + k_2)e_0}{k_- + k_2 + k_+ s} = e_0 \frac{K_m}{s + K_m} \text{ (the qss approximation)}$$

Furthermore, the "slow reaction" is

$$\frac{dp}{dt} = -\frac{ds}{dt} = k_2c = k_2e_0 \frac{s}{K_m + s}$$

This is called the Michaelis-Menten reaction rate, and is used routinely (without checking the underlying hypotheses).

Remark: An understanding of how to do fast-slow reductions is crucial!
1) Enzyme activity can be inhibited (or poisoned). For example,

\[ \begin{align*} 
S + E & \rightleftharpoons C \xrightarrow{k_2} P + E \\
I + E & \rightleftharpoons C_2 
\end{align*} \]

Then,

\[ \frac{dp}{dt} = -\frac{ds}{dt} = k_2 e_0 \frac{s}{s + K_m (1 + \frac{i}{K_i})} \]

2) Enzymes can have more than one binding site, and these can "cooperate".

\[ \begin{align*} 
S + E & \rightleftharpoons C_1 \xrightarrow{k_2} P + E \\
S + C_1 & \rightleftharpoons C_2 \xrightarrow{k_4} P + E 
\end{align*} \]

\[ \frac{dp}{dt} = -\frac{ds}{dt} = V_{max} \frac{s^2}{K_m^2 + s^2} \]
Introductory Biochemistry

- DNA, nucleotides, complementarity, codons, genes, promoters, repressors, polymerase, PCR
- mRNA, tRNA, amino acids, proteins
- ATP, ATPase, hydrolysis, phosphorylation, kinase, phosphatase
Biochemical Regulation

polymerase binding site
"start"
regulator region

Repressor bound

Polymerase bound

DNA → mRNA → E → trp

R* → R
P* → P

E
The Tryptophan Repressor

\[ \frac{dM}{dt} = k_m P - k_{-m} M, \]
\[ \frac{dE}{dt} = k_e M - k_{-e} E, \]
\[ \frac{dR^*}{dt} = k_R T^2 R - k_{-R} R^*, \quad R + R^* = R_0 \]
\[ \frac{dP}{dt} = k_{on} R^* P - k_{off} (1 - P) \]
\[ \frac{dT}{dt} = k_T E - k_{-T} T - 2 \frac{dR^*}{dt} \]
Steady State Analysis

\[ E(T) = \frac{k_e}{k_{-e}} \frac{k_m}{k_{-m}} \frac{k_{on}}{k_{off}} R^*(T) + 1 = k_{-T} T, \]

\[ R^*(T) = \frac{k_R T^2 R_0}{k_R T^2 + k_{-R}} \]

Simple example of Negative Feedback.
The Lac Operon

CAP binding site

RNA-polmerase binding site

start site

-operator

lac gene

+ glucose
+ lactose

operon off
(CAP not bound)

+ glucose
- lactose

operon off
(repressor bound)
(CAP not bound)

- glucose
- lactose

operon off
(repressor bound)

- glucose
+ lactose

operon on
The Lac Operon

- lactose
- outside the cell
- glucose
- lac permease
- lac operon
- repressor
- CAP
- cAMP
- +
- -
- lactose
- allolactose
## Lac Operon

\[
\begin{align*}
\frac{dM}{dt} &= \alpha_M \frac{1 + K_1 A^2}{K + K_1 A^2} - \gamma_M M, \\
\frac{dP}{dt} &= \alpha_P M - \gamma_P P, \\
\frac{dB}{dt} &= \alpha_B M - \gamma_B B, \\
\frac{dL}{dt} &= \alpha_L P \frac{L_e}{K_{Le} + L_e} - \alpha_A B \frac{L}{K_L + L} - \gamma_L L, \\
\frac{dA}{dt} &= \alpha_A B \frac{L}{K_L + L} - \beta_A B \frac{A}{K_A + A} - \gamma_A A.
\end{align*}
\]
Lac Operon - Simplified System

(P and B is qss, L instantly converted to A)

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\]
\[
\frac{dA}{dt} = \alpha_L \frac{\alpha_P}{\gamma_P} M \frac{L_e}{K_{Le} + L_e} - \beta_A \frac{\alpha_B}{\gamma_B} M \frac{A}{K_A + A} - \gamma_A A.
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\]

Large \( L_e \)
Lac Operon - Bifurcation Diagram
Circadian Rhythms

(Tyson, Hong, Thron, and Novak, Biophys J, 1999)
Circadian Rhythms

\[
\frac{dM}{dt} = \frac{v_m}{1 + \left(\frac{P_2}{A}\right)^2} - k_m M
\]

\[
\frac{dP}{dt} = v_p M - \frac{k_1 P_1 + 2k_2 P_2}{J + P} - k_3 P
\]

where \( q = \frac{2}{1 + \sqrt{1 + 8KP}} \), \( P_1 = qP \), \( P_2 = \frac{1}{2}(1 - q)P \).
Other Interesting Oscillatory Networks

Glycolytic Oscillations (K&S 1998)

Cell Cycle (K&S 1998)