Introduction to Mathematical Physiology
I - Biochemical Reactions

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Introduction

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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Examples:
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* - find the slope of a function (Mathematician)
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- to differentiate - change the function of a cell (Biologist)
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- a **PDE** -
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Examples:

• to divide - replicate the contents of a cell and split into two (Biologist)

• to differentiate - change the function of a cell (Biologist)

• a PDE - Partial Differential Equation (Mathematician)
A few words about words

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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

- The study of biological processes is over many space and time scales (roughly $10^{16}$):
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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
Some Biological Challenges

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- Populations and ecosystems - biodiversity, extinction, invasions
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:

$$\frac{d}{dt} \int_{\Omega} udV = \int_{\partial \Omega} J \cdot n ds + \int_{\Omega} f dv$$

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,

\[ A + C \leftrightarrow B \]

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

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 \(a\).
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.)

\[
\text{O}_2 \quad \text{CO}_2
\]

In Tissue

\[
\text{O}_2 \quad \text{CO}_2
\]

In Lungs
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.)

\[
\text{In Tissue} \\
\begin{align*}
\text{O}_2 & \quad \text{CO}_2 \\
\text{HbO}_4^+ & \quad \text{HCO}_3^- \quad \text{H}^- \\
\end{align*}
\]

\[
\text{In Lungs} \\
\begin{align*}
\text{O}_2 & \quad \text{CO}_2 \\
\text{HbO}_4^+ & \quad \text{HCO}_3^- \quad \text{H}^- \\
\end{align*}
\]

Problem solved: Chemical reactions that help enormously:

\[
\text{CO}_2(+\text{H}_2\text{O}) \leftrightarrow \text{HCO}_3^+ + \text{H}^- \quad \text{Hb} + 4\text{O}_2 \leftrightarrow \text{Hb(O}_2)^4
\]
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.)

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\[ CO_2 (+H_2O) \leftrightarrow HCO_3^- + H^- \]

\[ Hb + 4O_2 \leftrightarrow Hb(O_2)^4 \]

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.
$S + E \xrightarrow{k_2} C \xrightarrow{k_2} P + E$

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

Use that $e + c = e_0$, so that

$$\frac{ds}{dt} = k_-(e_0 - e) - k_+ se$$
$$\frac{de}{dt} = -k_+ se + (k_- + k_2)(e_0 - e)$$
Assume that the equation for $e$ is "fast", and so in quasi-equilibrium. Then,

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

or

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

Furthermore, the "slow reaction" is

$$\frac{dp}{dt} = -\frac{ds}{dt} = k_2 c = k_2 e_0 \frac{s}{K_m + s}$$

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,

\[ S + E \xleftrightarrow{\kappa_2} C \xrightarrow{ \kappa_2 } P + E \quad I + E \xleftrightarrow{} C_2 \]

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".

\[ S + E \xleftrightarrow{} C_1 \xrightarrow{ \kappa_2 } P + E \quad S + C_1 \xleftrightarrow{} C_2 \xrightarrow{ \kappa_4 } P + E \]

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

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

![Diagram of biochemical regulation](image_url)

- Polymerase binding site
- "start"
- Regulator region
- Repressor bound
- Polymerase bound
- DNA → mRNA → E → trp pathway
- $R^*$ → $R$
- $O_l$ ↔ $O_R$

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The Tryptophan Repressor

\[
\begin{align*}
\frac{dM}{dt} &= k_m O_P - k_{-m} M, \\
\frac{dO_P}{dt} &= k_{on} O_f - k_{off} O_P, \quad O_f + O_P + O_R = 1, \\
\frac{dO_R}{dt} &= k_r R^* O_f - k_{-r} O_R, \\
\frac{dR^*}{dt} &= k_R T^2 R - k_{-R} R^*, \quad R + R^* = R_0 \\
\frac{dE}{dt} &= k_e M - k_{-e} E, \\
\frac{dT}{dt} &= k_T E - k_{-T} T - 2 \frac{dR^*}{dt}
\end{align*}
\]
Steady State Analysis

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

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

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)
- glucose - lactose: operon off (repressor bound)
- glucose + lactose: operon on
The Lac Operon

\[
R + 2A \rightleftharpoons R_I, \quad O + R \rightleftharpoons O_I, \\
O \rightarrow M \rightarrow E, P, \quad P \rightarrow L \rightarrow A
\]
Lac Operon

\[
\begin{align*}
\frac{dM}{dt} &= \alpha_M O - \gamma_M M, \\
O &= \frac{1 + K_1 A^2}{K + K_1 A^2} \quad \text{(qss assumption)} \quad \text{(-2)} \\
\frac{dP}{dt} &= \alpha_P M - \gamma_P P, \\
\frac{dE}{dt} &= \alpha_E M - \gamma_E E, \\
\frac{dL}{dt} &= \alpha_L P \frac{L_e}{K_{Le} + L_e} - \alpha_A E \frac{L}{K_L + L} - \gamma_L L, \\
\frac{dA}{dt} &= \alpha_A E \frac{L}{K_L + L} - \beta_A E \frac{A}{K_A + A} - \gamma_A A.
\end{align*}
\]
Lac Operon - Simplified System

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

\[
\frac{dM}{dt} = \alpha_M \frac{1 + K_1 A^2}{K + K_1 A^2} - \gamma_M M,
\]

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

Small \(L_e\)
Lac Operon - Simplified System

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

\[
\frac{dM}{dt} = \alpha_M \frac{1 + K_1 A^2}{K + K_1 A^2} - \gamma_M M,
\]

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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_E}{\gamma_E} M \frac{A}{K_A + A} - \gamma_A A.
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\]
Lac Operon - Bifurcation Diagram

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Glycolysis

\[ \gamma S_2 + E \stackrel{k_3}{\rightleftharpoons} ES_2^{\gamma}, \quad (S_2 = ADP) \]

\[ S_1 + ES_2^{\gamma} \stackrel{k_1}{\rightleftharpoons} S_1ES_2^{\gamma} \stackrel{k_2}{\rightarrow} ES_2^{\gamma} + S_2, \]

\[ S_2 \stackrel{v_2}{\rightarrow}. \]
Glycolysis

\[
\begin{align*}
\gamma S_2 + E & \overset{k_3}{\underset{k_3}{\rightleftharpoons}} ES_2^\gamma \\
& \overset{v_1}{\rightarrow} S_1 \\
S_1 + ES_2^\gamma & \overset{k_1}{\underset{k_1}{\rightleftharpoons}} S_1ES_2^\gamma \overset{k_2}{\rightarrow} ES_2^\gamma + S_2, \\
S_2 & \overset{v_2}{\rightarrow}.
\end{align*}
\]

Applying the law of mass action:

\[
\begin{align*}
\frac{ds_1}{dt} &= v_1 - k_1 s_1 x_1 + k_{-1} x_2, \\
\frac{ds_2}{dt} &= k_2 x_2 - \gamma k_3 s_2^\gamma e + \gamma k_{-3} x_1 - v_2 s_2, \\
\frac{dx_1}{dt} &= -k_1 s_1 x_1 + (k_{-1} + k_2) x_2 + k_3 s_2^\gamma e - k_{-3} x_1, \\
\frac{dx_2}{dt} &= k_1 s_1 x_1 - (k_{-1} + k_2) x_2.
\end{align*}
\]
Nondimensionalize and apply qss:

\[
\begin{align*}
\frac{d\sigma_1}{d\tau} &= \nu - f(\sigma_1, \sigma_2), \\
\frac{d\sigma_2}{d\tau} &= \alpha f(\sigma_1, \sigma_2) - \eta \sigma_2,
\end{align*}
\]

where

\[
\begin{align*}
u_1 &= \frac{\sigma_2^\gamma}{\sigma_2^\gamma \sigma_1 + \sigma_2^\gamma + 1}, \\
\nu_2 &= \frac{\sigma_1 \sigma_2^\gamma}{\sigma_2^\gamma \sigma_1 + \sigma_2^\gamma + 1} = f(\sigma_1, \sigma_2).
\end{align*}
\]
Circadian Rhythms

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

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

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

where \( q = \frac{2}{1 + \sqrt{1 + 8KP}} \), \( P_1 = qP \), \( P_2 = \frac{1}{2}(1 - q)P \).
Cell Cycle (K&S 1998)