Imagine the Possibilities

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Introduction to Mathematical Physiology I - Biochemical Reactions

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Introduction

The Dilemma of Modern Biology

- The amount of data being collected is staggering. Knowing what to do with the data is in its infancy.
- 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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A few words about words

A big difficulty in communication between Mathematicians and Biologists is because of different vocabulary.

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- to divide - find the ratio of two numbers (Mathematician)

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

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- to divide - replicate the contents of a cell and split into two (Biologist)
- 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 - Partial Differential Equation (Mathematician)

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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).

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- Space scales: Genes → proteins → networks→ cells→ tissues and organs → organism → communities → ecosystems
- Time scales: protein conformational changes → protein folding → action potentials → hormone secretion → protein translation → cell cycle → circadian rhythms → human disease processes → population changes → evolutionary scale adaptation

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- Multicellularity - organs, tissues, organisms, morphogenesis
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- Populations and ecosystems- biodiversity, extinction, invasions

Introduction

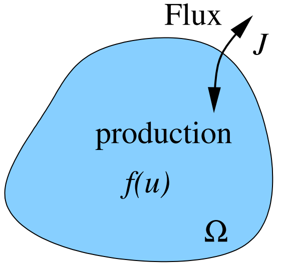
Biology is characterized by change. A major goal of modeling is to quantify how things change.

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 Ω, f is the production rate density, and Ω 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,

$$A \rightleftarrows B$$

then

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

At steady state,

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

Bimolecular Chemical Reactions

$$A + C \stackrel{k}{\rightarrow} B$$

then

$$\frac{da}{dt} = -kca = -\frac{db}{dt} \qquad \text{(the "law" of mass action).}$$

With back reactions,

$$A + C \rightleftarrows B$$

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

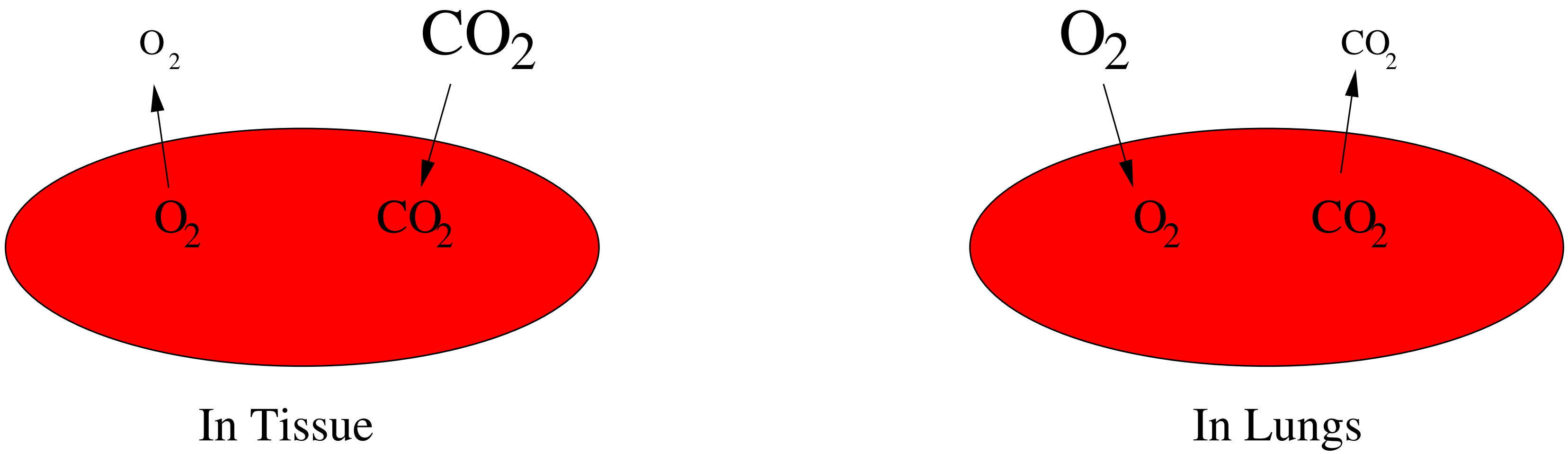
In steady state, $-k_+ca + k_-b = 0$ and $a + b = a_0$, so that

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

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.)



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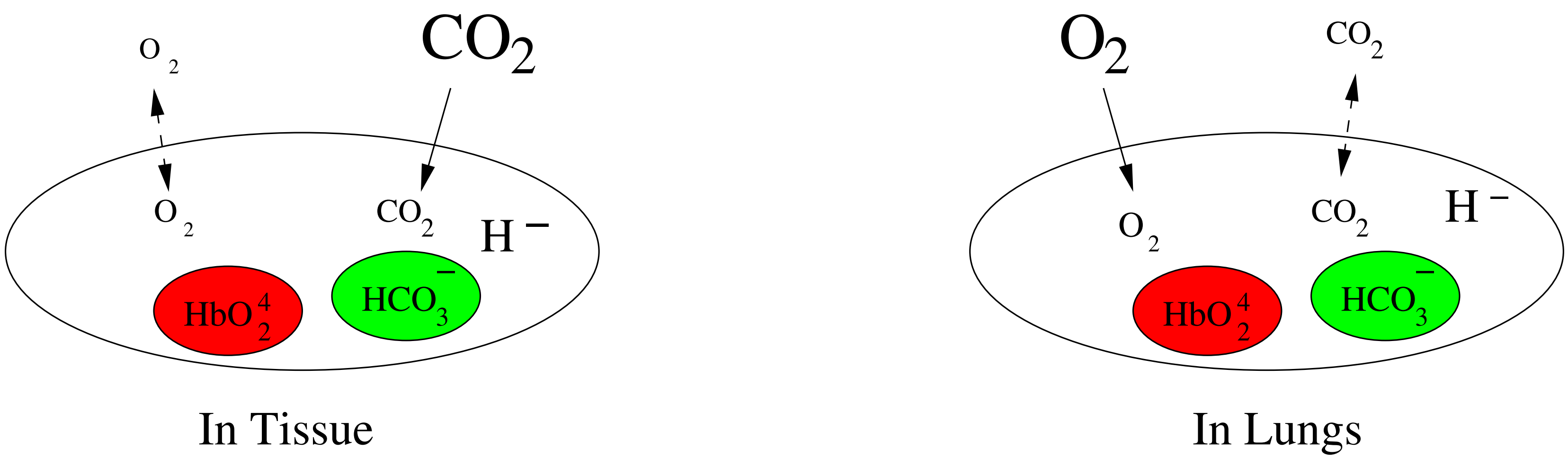


Problem solved: Chemical reactions that help enormously:

$$CO_2(+H_2O) \rightleftarrows HCO_3^+ + H^- \qquad Hb + 4O_2 \rightleftarrows Hb(O_2)^4$$

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.)

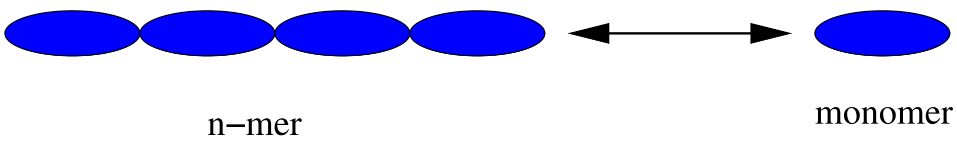
In Tissue   In Lungs

Problem solved: Chemical reactions that help enormously:

$$CO_2(+H_2O) \rightleftarrows HCO_3^+ + H^- \qquad Hb + 4O_2 \rightleftarrows Hb(O_2)^4$$

Hydrogen competes with oxygen for hemoglobin binding.

Example II: Polymerization



$$A_n + A_1 \rightleftarrows A_{n+1}$$

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

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

$$S + E \rightleftarrows C \overset{k_2}{\rightarrow} P + E$$

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

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

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

The QSS Approximation

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

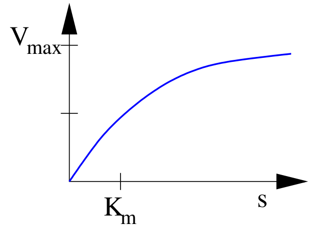
$$(k_- + k_2)(e_0 - e) - k_+ s e = 0$$

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

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



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!

Enzyme Interactions

1) Enzyme activity can be inhibited (or poisoned). For example,

$$S + E \rightleftarrows C \overset{k_2}{\rightarrow} P + E \qquad I + E \rightleftarrows C_2$$

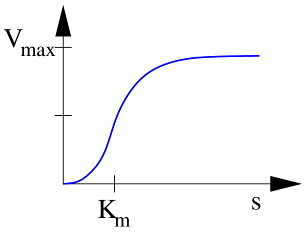
Then,

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

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

$$S + E \rightleftarrows C_1 \overset{k_2}{\rightarrow} P + E \qquad S + C_1 \rightleftarrows C_2 \overset{k_4}{\rightarrow} P + E$$

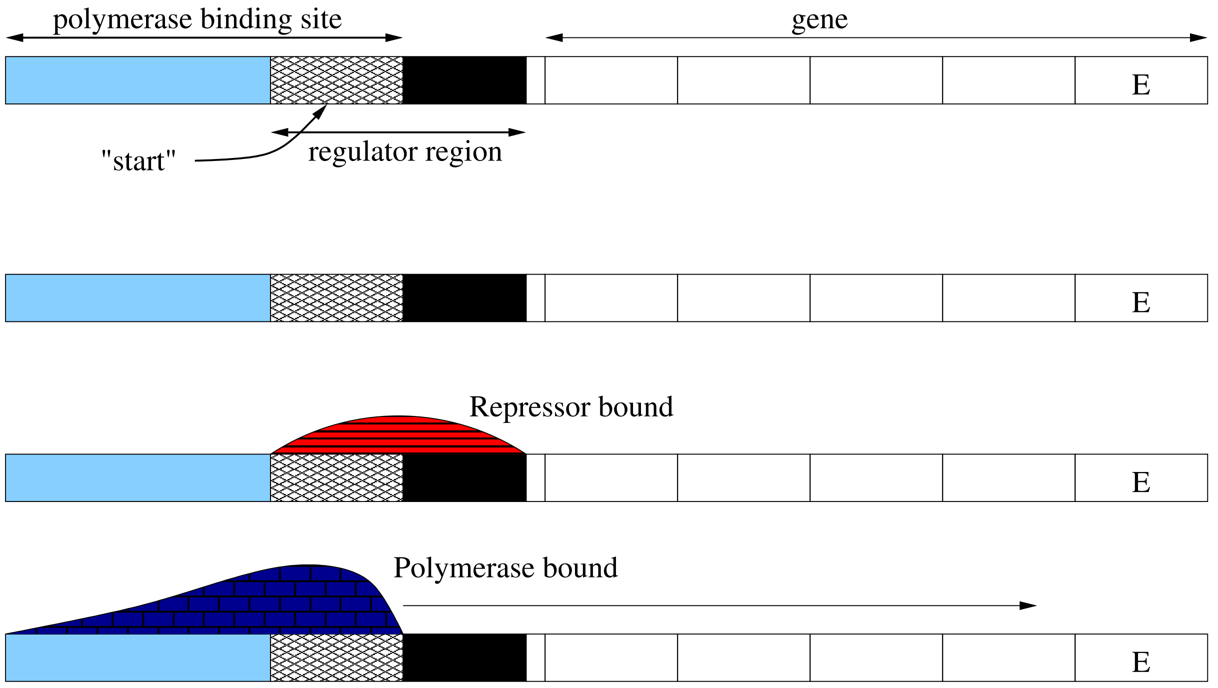
$$\frac{dp}{dt} = -\frac{ds}{dt} = V_{max} \frac{s^2}{K_m^2 + s^2}$$

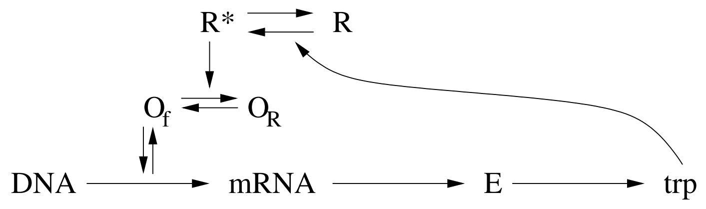


Introductory Biochemistry

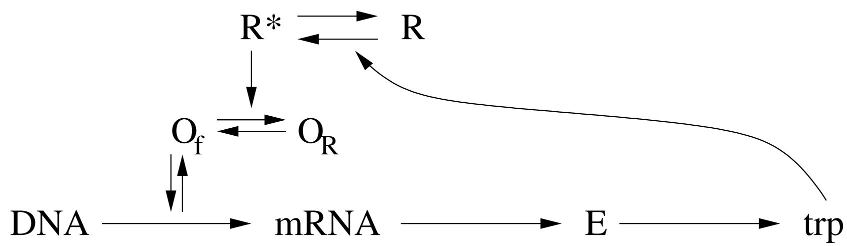
- DNA, nucleotides, complementarity, codons, genes, promoters, repressors, polymerase, PCR
- mRNA, tRNA, amino acids, proteins
- ATP, ATPase, hydrolysis, phosphorylation, kinase, phosphatase

Biochemical Regulation





The Tryptophan Repressor



$$\frac{dM}{dt} = k_m O_P - k_{-m} M,$$

$$\frac{dO_P}{dt} = k_{on} O_f - k_{off} O_P, \qquad O_f + O_P + O_R = 1,$$

$$\frac{dO_R}{dt} = k_r R^* O_f - k_{-r} O_R,$$

$$\frac{dR^*}{dt} = k_R T^2 R - k_{-R} R^*, \qquad R + R^* = R_0$$

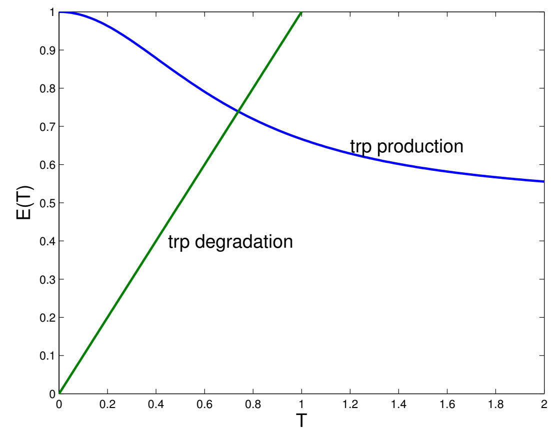
$$\frac{dE}{dt} = k_e M - k_{-e} E,$$

$$\frac{dT}{dt} = k_T E - k_{-T} T - 2\frac{dR^*}{dt}$$

Steady State Analysis

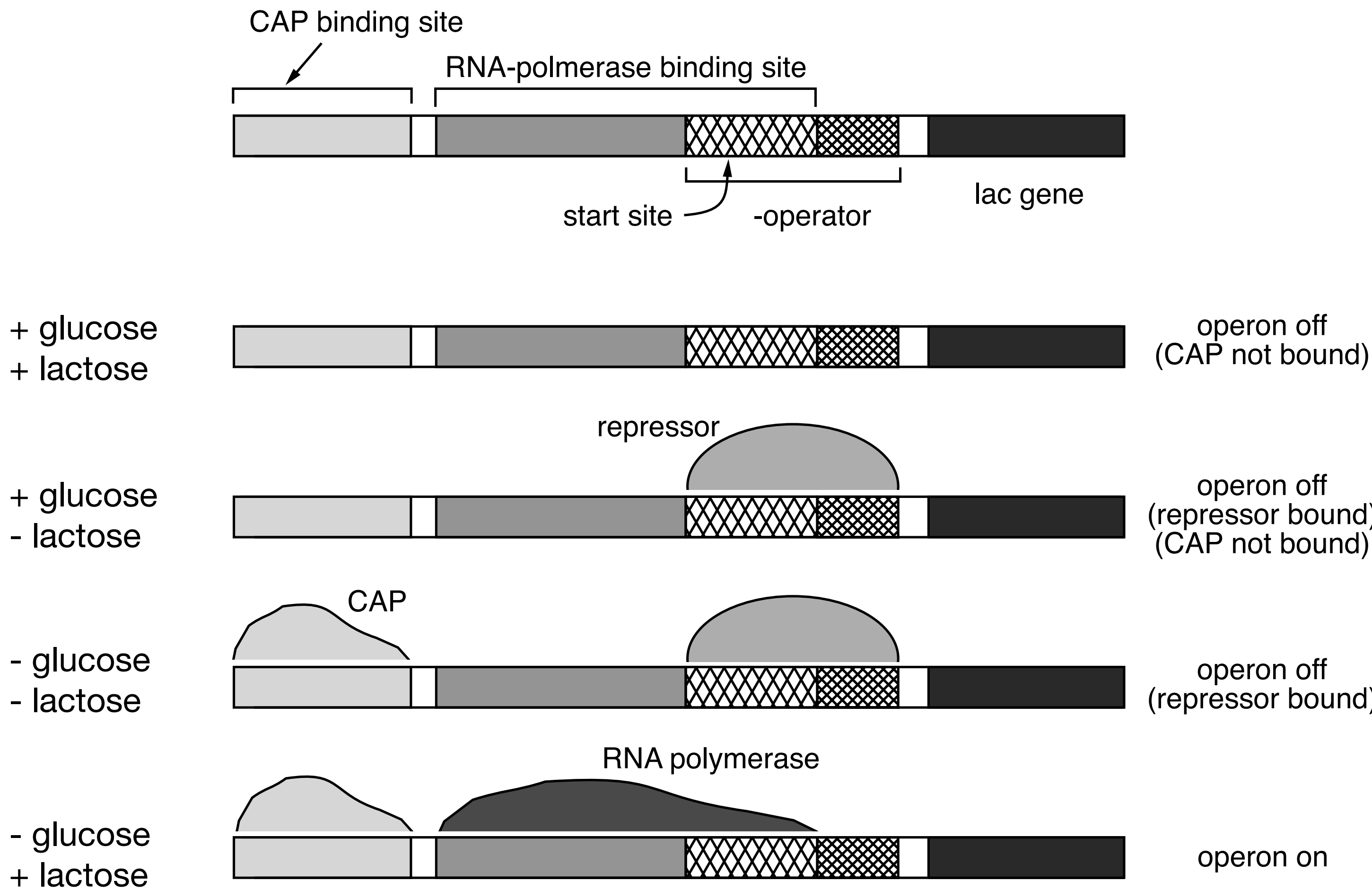
$$E(T) = \frac{k_e}{k_{-e}} \frac{k_m}{k_{-m}} \frac{1}{\frac{k_{on}}{k_{off}} R^*(T) + 1} = k_{-T} T,$$

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



Simple example of Negative Feedback.

The Lac Operon



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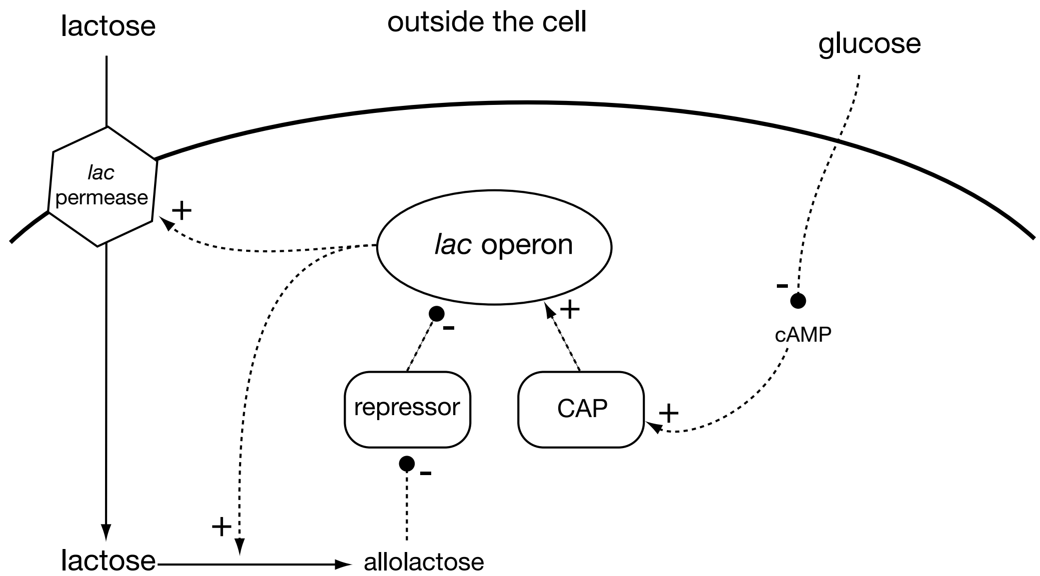


$$R + 2A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R_I, \qquad O + R \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} O_I,$$

$$O \to M \to E, P, \qquad P \to L \xrightarrow{E} A$$

Lac Operon

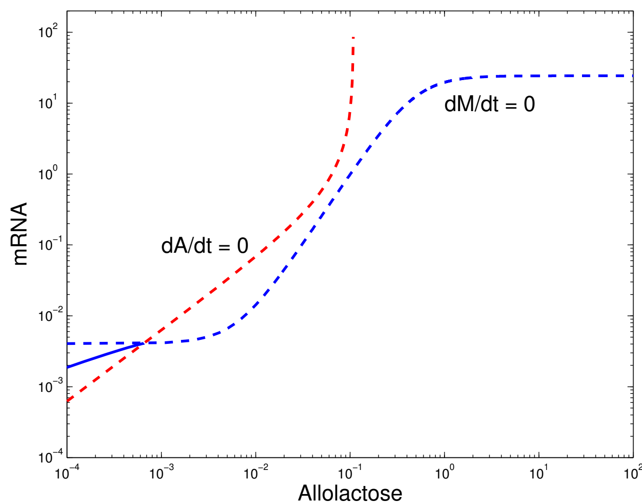
$$
\begin{aligned}
\frac{dM}{dt} &= \alpha_M O - \gamma_M M, \\
O &= \frac{1 + K_1 A^2}{K + K_1 A^2} \qquad \text{(qss assumption)} \\
\frac{dP}{dt} &= \alpha_P M - \gamma_P P, \\
\frac{dE}{dt} &= \alpha_E M - \gamma_E E, \\
\frac{dL}{dt} &= \alpha_L P \frac{L_e}{K_{Le} + L_e} - \alpha_A E \frac{L}{K_L + L} - \gamma_L L, \\
\frac{dA}{dt} &= \alpha_A E \frac{L}{K_L + L} - \beta_A E \frac{A}{K_A + A} - \gamma_A A.
\end{aligned} \tag{-2}
$$

Lac Operon - Simplified System

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

$$\frac{dM}{dt} = \alpha_M \frac{1+K_1A^2}{K+K_1A^2} - \gamma_M M,$$

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



Small L_e

Lac Operon - Simplified System

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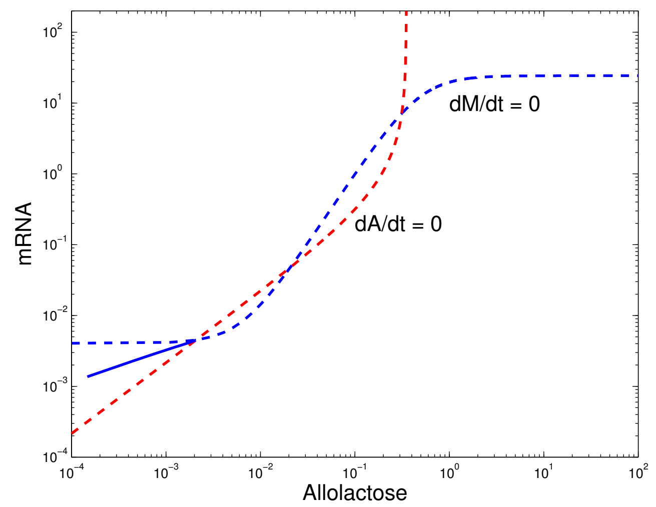


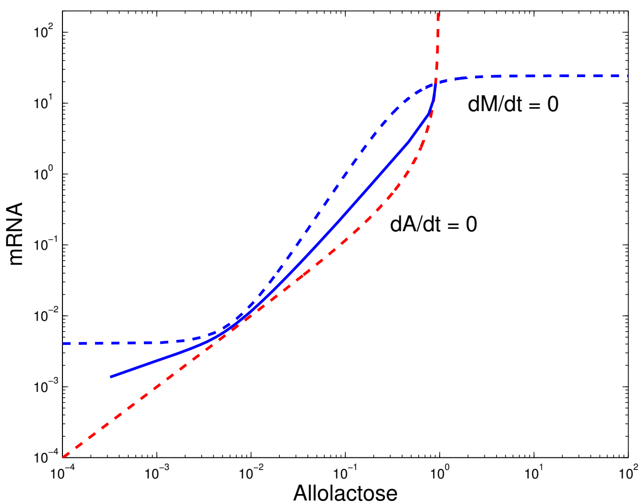
Intermediate L_e

Lac Operon - Simplified System

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

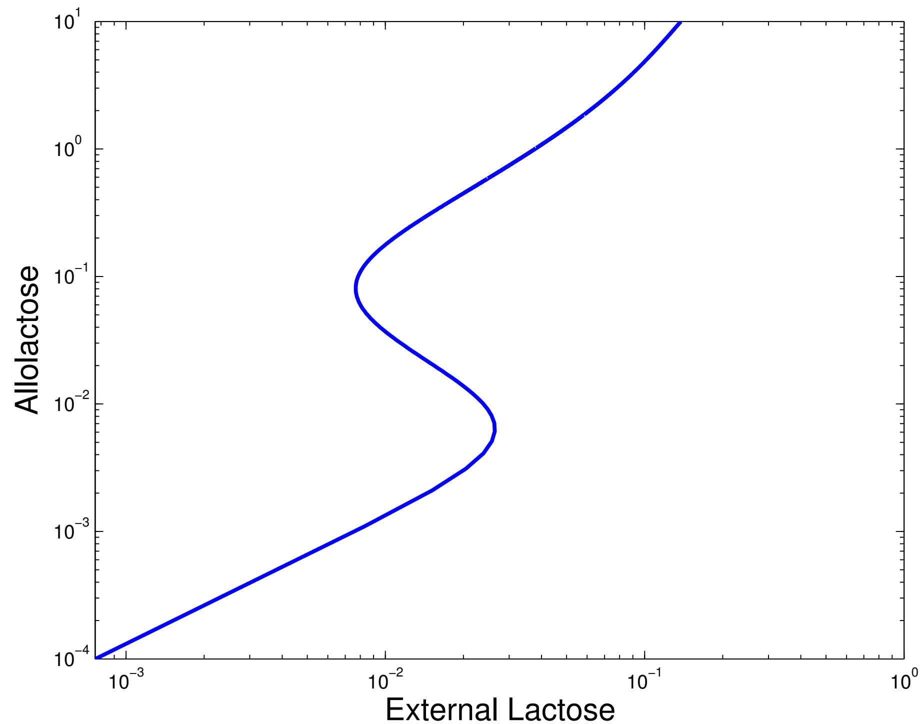
$$\frac{dM}{dt} = \alpha_M \frac{1 + K_1 A^2}{K + K_1 A^2} - \gamma_M M,$$

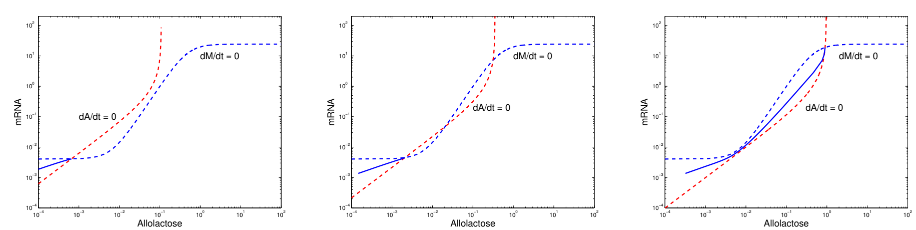
$$\frac{dA}{dt} = \alpha_L \frac{\alpha_P}{\gamma_P} M \frac{L_e}{K_{Le} + L_e} - \beta_A \frac{\alpha_E}{\gamma_E} M \frac{A}{K_A + A} - \gamma_A A.$$



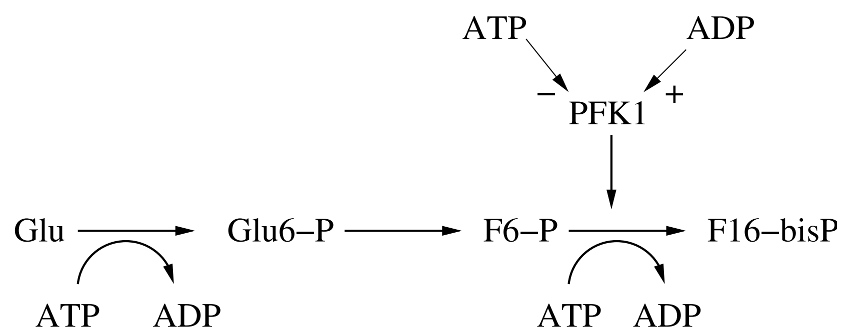
Large L_e

Lac Operon - Bifurcation Diagram





Glycolysis



$$
\begin{aligned}
\gamma \mathrm{S}_2 + \mathrm{E} \quad & \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} \quad \mathrm{ES}_2^\gamma, \qquad (\mathrm{S}_2 = \mathrm{ADP}) \\
& \xrightarrow{v_1} \quad \mathrm{S}_1, \qquad (\mathrm{S}_1 = \mathrm{ATP}) \\
\mathrm{S}_1 + \mathrm{ES}_2^\gamma \quad & \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \quad \mathrm{S}_1\mathrm{ES}_2^\gamma \xrightarrow{\mathrm{k}_2} \mathrm{ES}_2^\gamma + \mathrm{S}_2, \\
\mathrm{S}_2 \quad & \xrightarrow{v_2}.
\end{aligned}
$$

Glycolysis

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&\xrightarrow{v_1} \quad \mathrm{S}_1 \\
\mathrm{S}_1 + \mathrm{ES}_2^\gamma \quad &\underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \quad \mathrm{S}_1\mathrm{ES}_2^\gamma \xrightarrow{\mathrm{k}_2} \mathrm{ES}_2^\gamma + \mathrm{S}_2, \\
\mathrm{S}_2 \quad &\xrightarrow{v_2}.
\end{aligned}$$

Applying the law of mass action:

$$\begin{aligned}
\frac{ds_1}{dt} &= v_1 - k_1 s_1 x_1 + k_{-1} x_2, \\
\frac{ds_2}{dt} &= k_2 x_2 - \gamma k_3 s_2^\gamma e + \gamma k_{-3} x_1 - v_2 s_2, \\
\frac{dx_1}{dt} &= -k_1 s_1 x_1 + (k_{-1} + k_2) x_2 + k_3 s_2^\gamma e - k_{-3} x_1, \\
\frac{dx_2}{dt} &= k_1 s_1 x_1 - (k_{-1} + k_2) x_2.
\end{aligned}$$

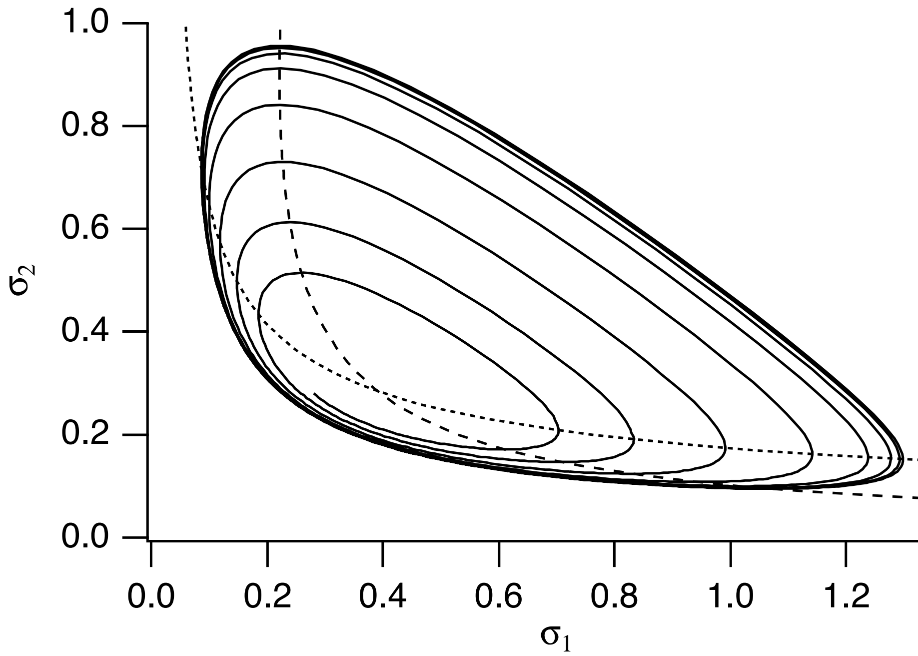
Glycolysis

Nondimensionalize and apply qss:

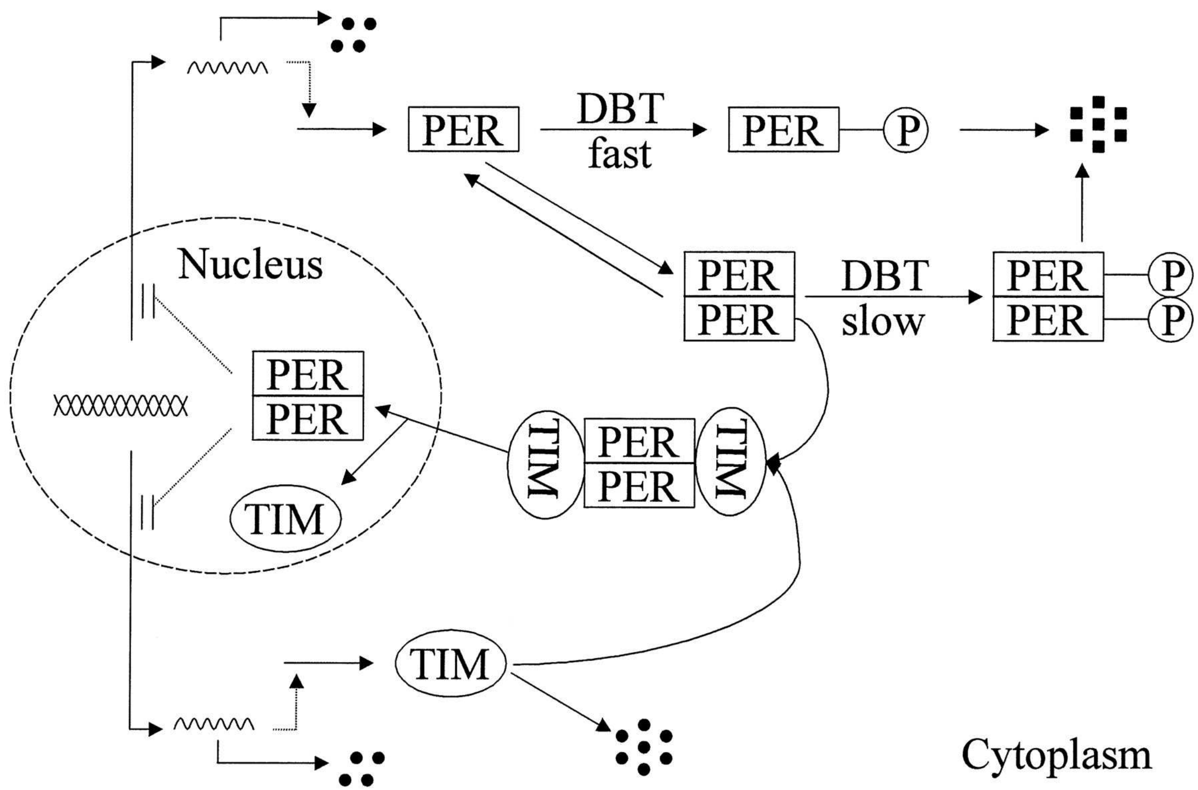
$$\frac{d\sigma_1}{d\tau} = \nu - f(\sigma_1, \sigma_2),$$
$$\frac{d\sigma_2}{d\tau} = \alpha f(\sigma_1, \sigma_2) - \eta\sigma_2,$$

where

$$u_1 = \frac{\sigma_2^\gamma}{\sigma_2^\gamma \sigma_1 + \sigma_2^\gamma + 1},$$
$$u_2 = \frac{\sigma_1 \sigma_2^\gamma}{\sigma_2^\gamma \sigma_1 + \sigma_2^\gamma + 1} = f(\sigma_1, \sigma_2).$$



Circadian Rhythms



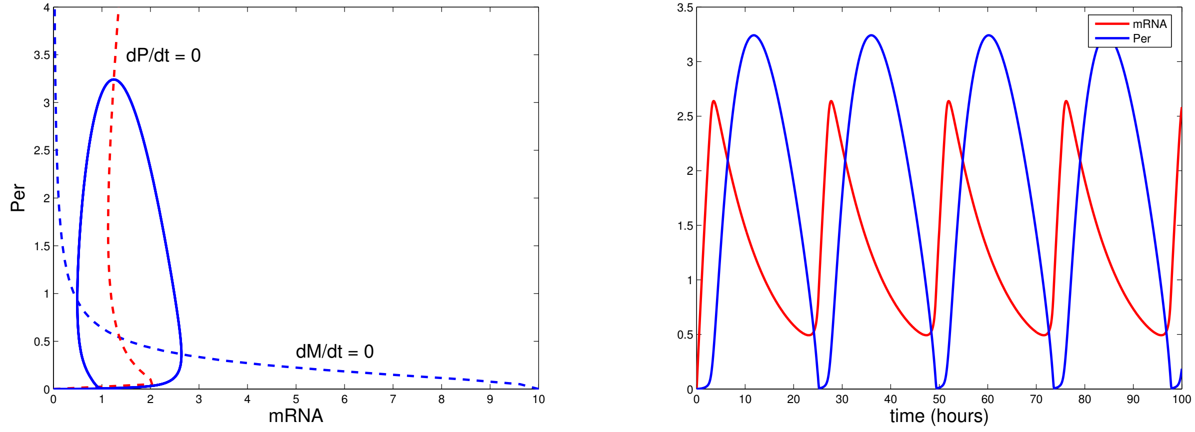
(Tyson, Hong, Thron, and Novak, Biophys J, 1999)

Circadian Rhythms

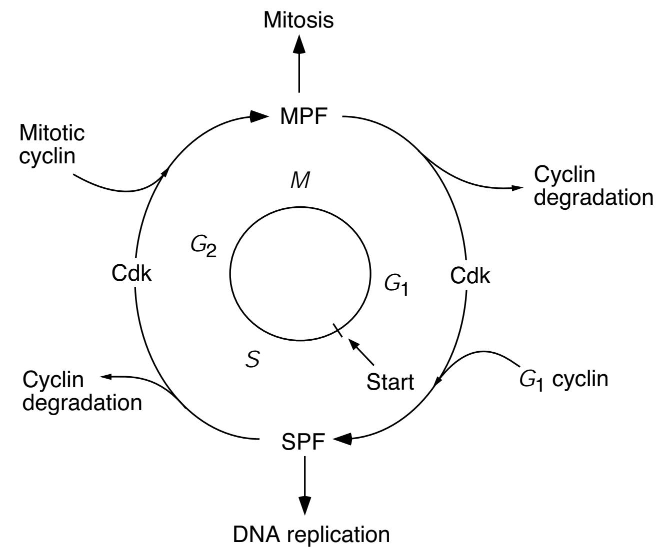
$$\frac{dM}{dt} = \frac{v_m}{1+\left(\frac{P_2}{A}\right)^2} - k_m M$$

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

where $q = 2/(1+\sqrt{1+8KP})$, $P_1 = qP$, $P_2 = \frac{1}{2}(1-q)P$.



Cell Cycle



Cell Cycle (K&S 1998)