

Introduction to Dynamical Systems

Part 1



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Outline

Modeling using ODEs

Law of mass action

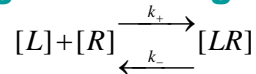
The Michaelis-Menten approximation for enzyme-catalyzed reactions

Converting from a diagram to a system of equations

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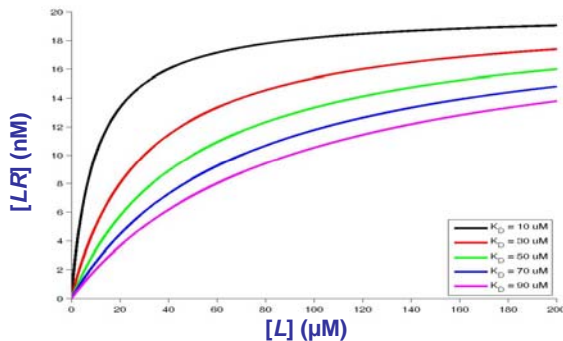
Systems of Ordinary Differential Equations

Consider ligand binding to a receptor



In the steady-state, bound receptor can be calculated as:

$$[LR] = \frac{R_{TOT} [L]}{K_D + [L]} \quad K_D = \frac{k_-}{k_+}$$



$[L]$ = free ligand

$[R]$ = free receptor

$[R]_{TOT}$ = total receptor

$[LR]$ = ligand-receptor complex

$R_{TOT} = 20 \text{ nM}$

$[L]$ varies from 0 to 200 μM

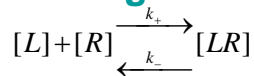
K_D can be 10, 30, 50, 70, 90 μM

What about non-steady-state solutions?

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Systems of Ordinary Differential Equations

Ligand binding to a receptor



More generally, this reaction implies the following set of equations

$$\frac{d[L]}{dt} = -k_+[L][R] + k_-[LR]$$

$$\frac{d[R]}{dt} = -k_+[L][R] + k_-[LR]$$

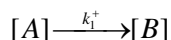
$$\frac{d[LR]}{dt} = k_+[L][R] - k_-[LR]$$

Where do these equations come from?

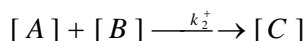
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Law of mass action

The rate of an elementary reaction (a reaction that proceeds through only one transition state, that is one mechanistic step) is proportional to the product of the concentrations of the participating molecules. (source: Wikipedia)



$$\text{Forward rate (concentration/time)} = k_1^+ [A]$$



$$\text{Forward rate} = k_2^+ [A][B]$$

$[A]$, $[B]$, $[C]$ = generic chemical species

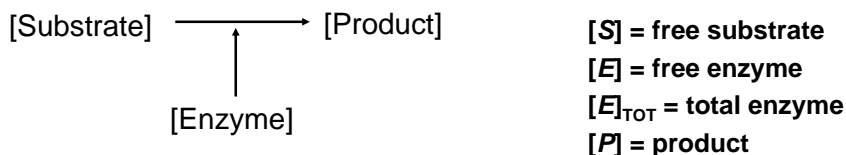
Note that rate constants k_1^+ and k_2^+ have different units

This allows us to write down equations for many reactions

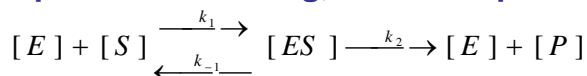
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Enzyme-catalyzed reactions

Frequently shorthand is used



This shorthand implies the following, more complete reaction scheme:



Michaelis-Menten kinetics are usually assumed

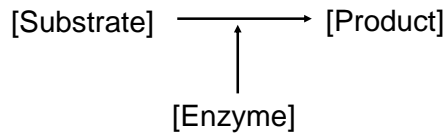
$$V_0 = \frac{dP}{dt} = \frac{V_{\max} [S]}{K_M + [S]}$$

with variable definitions:

$$V_{\max} = k_2 [E]_{\text{TOT}} \quad K_M = \frac{k_{-1} + k_2}{k_1}$$

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Enzyme-catalyzed reactions



$[S]$ = free substrate
 $[E]$ = free enzyme
 $[E]_{\text{TOT}}$ = total enzyme
 $[P]$ = product

If Michaelis-Menten kinetics are assumed, the relevant ODEs become:

$$\frac{d[S]}{dt} = -k_{\text{cat}} [E] \frac{[S]}{[S] + K_m}$$

$$\frac{d[P]}{dt} = k_{\text{cat}} [E] \frac{[S]}{[S] + K_m}$$

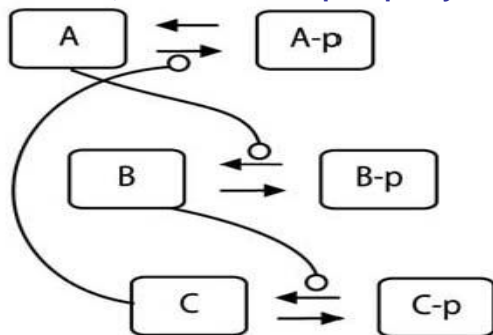
k_{cat} = catalytic constant of enzyme, called k_2 in previous slide

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More complicated biochemical reactions

Example: a generic three component repressive network
 this can display oscillations, depending on parameter values

Proteins A, B and C can be phosphorylated (X-p) or dephosphorylated (X)



A catalyzes dephosphorylation of B
 B catalyzes dephosphorylation of C
 C catalyzes phosphorylation of A

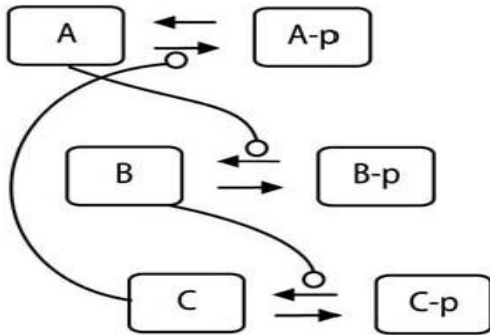
Mogilner et al., *Developmental Cell* 11:279–287, 2006

Note: This scheme is a simplified version of an oscillatory biochemical circuit in soil bacteria (see Igoshin et al., *PNAS* 101:15760–15765, 2004)

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More complicated biochemical reactions

The full set of equations underlying this scheme



$$\frac{d[A]}{dt} = \frac{k_{p1}([A]_T - [A])}{[A]_T - [A] + K_{p1}} - \frac{k_{k1}[A][C]}{[A] + K_{k1}}$$

$$\frac{d[B]}{dt} = \frac{k_{p2}([B]_T - [B])[A]}{[B]_T - [B] + K_{p2}} - \frac{k_{k2}[B]}{[B] + K_{k2}}$$

$$\frac{d[C]}{dt} = \frac{k_{p3}([C]_T - [C])[B]}{[C]_T - [C] + K_{p3}} - \frac{k_{k3}[C]}{[C] + K_{k3}}$$

Mogilner et al., *Developmental Cell* 11:279–287, 2006

Two questions we need to address:

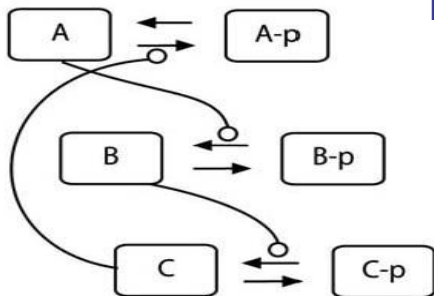
- (1) Why only 3 equations rather than 6?
- (2) Why do the 3 equations share a characteristic structure?

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More complicated biochemical reactions

Example: a generic three-component repressive network

Equations just for [A] and [AP]



$$\frac{d[A]}{dt} = \frac{k_{p1}[AP]}{[AP] + K_{p1}} - \frac{k_{k1}[A][C]}{[A] + K_{k1}}$$

$$\frac{d[AP]}{dt} = \frac{k_{k1}[A][C]}{[A] + K_{k1}} - \frac{k_{p1}[AP]}{[AP] + K_{p1}}$$

substrate
enzyme
 K_m

Mogilner et al., *Developmental Cell*
11:279–287, 2006

Notice that:

$$\frac{d[A]}{dt} = -\frac{d[AP]}{dt} \quad \text{Same as: } [A] + [AP] = [A]_T$$

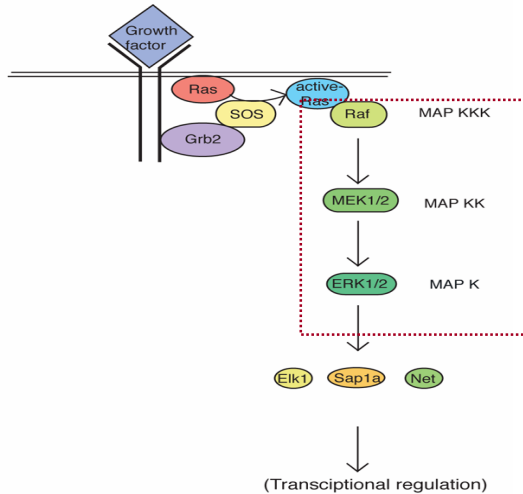
One equation can be eliminated, substitute: $[AP] = [A]_T - [A]$

$$\frac{d[A]}{dt} = \frac{k_{p1}([A]_T - [A])}{[A]_T - [A] + K_{p1}} - \frac{k_{k1}[A][C]}{[A] + K_{k1}}$$

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More complicated biochemical reactions

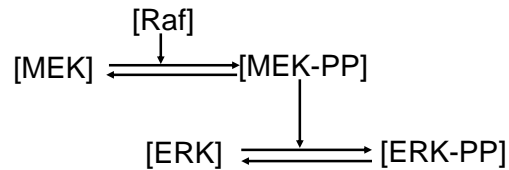
Sometimes the shorthand is even more extreme



Summary of Map kinase pathway

Diagram from the RIKEN BioResource Center:
<http://www.brc.riken.jp/>

What this really means is:



Equations can be derived from this scheme, not from scheme on the left

[Raf], [MEK], [ERK] = proteins involved in mitogen-activated protein kinase signaling

[-PP] = doubly phosphorylated form

Sometimes considerable prior biological knowledge is required to derive equations from cartoons describing mechanisms.

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Summary

Biochemical signaling pathways can usually be described mathematically with systems of ODEs

Writing down the relevant ODEs is the first step in constructing a model.

Biochemical signaling ODEs are generally some combination of:

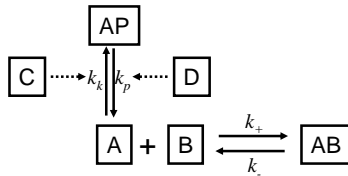
Law of mass action for simple reactions

Michaelis-Menten approximations for enzyme-catalyzed reactions

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Self-assessment question

Consider the reaction scheme below. Proteins **A** and **B** can bind to form complex **AB**. When it is free, but not when it is bound to **B**, protein **A** can be phosphorylated. Phosphorylated **A**, **A-P**, can be dephosphorylated. Phosphorylation and dephosphorylation reactions, respectively, are catalyzed by proteins **C** and **D**. These two proteins, respectively, have K_M 's K_k and K_p (for kinase and phosphatase). Rate constants are as listed. Which is the correct ODE for **A**, the unbound, dephosphorylated form of the protein?



(A)
$$\frac{d[A]}{dt} = -\frac{k_k[D][A]}{[A] + K_k} + \frac{k_p[D][AP]}{[A] + K_k} - k_+[A][B] + k_-[AB]$$

(B)
$$\frac{d[A]}{dt} = \frac{k_k[C][A]}{[A] + K_k} - \frac{k_p[D][AP]}{[AP] + K_p}$$

(C)
$$\frac{d[A]}{dt} = -\frac{k_k[C][A]}{[A] + K_k} + \frac{k_p[D][AP]}{[AP] + K_p} - k_+[A][B] + k_-[AB]$$

(D)
$$\frac{d[A]}{dt} = -k_+[A][B] + k_-[AB]$$