Mathematical Cell Biology Graduate Summer Course

University of British Columbia, May 1-31, 2012

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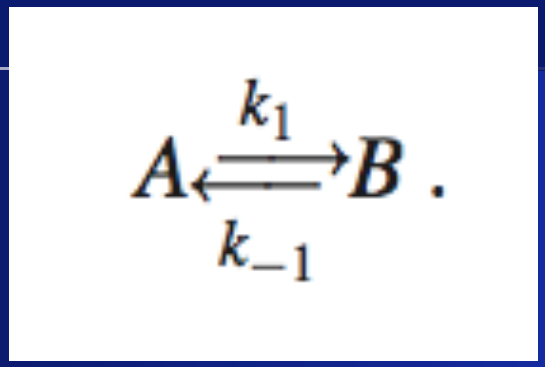
Modeling Preliminaries

Simple biochemical models,
The Law of Mass Action,
and Michaelis-Menten Kinetics

State transitions and rate equations



Consider a small time interval of duration Δt.

Initially: state A.

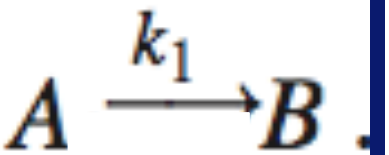
During an interval Δt either

(i) the molecule remains in state A, or

(ii) the molecule shifts to state B and stays in state B.

We define $k_1 \Delta$t to be the probability of (ii)

Transition probability

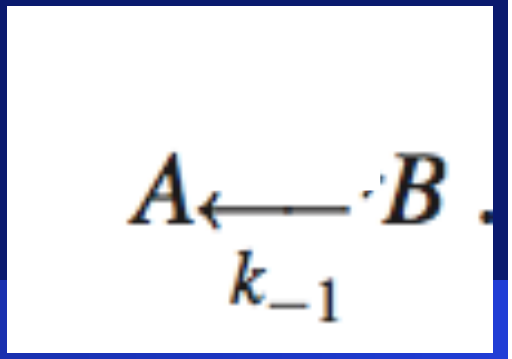


Probability that during an interval of duration Δt a molecule that is initially in state A will shift to state B:

Prob = $k_1 \Delta t [1 + E(\Delta t)]$

Small error term that approaches 0 as Δt gets small

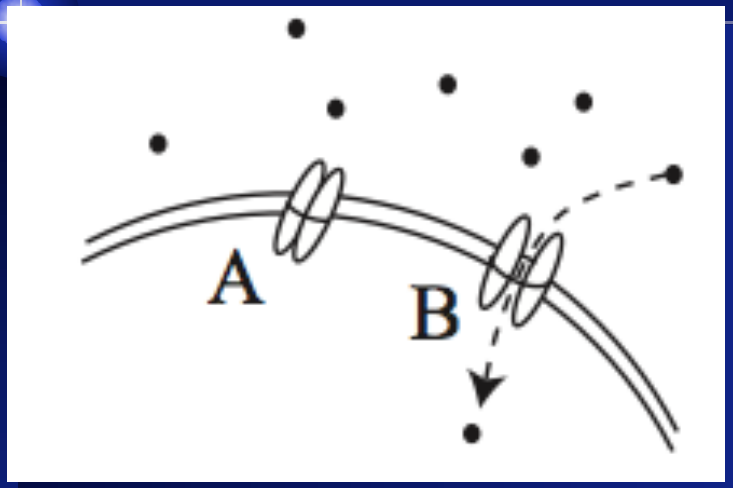
Transition probability



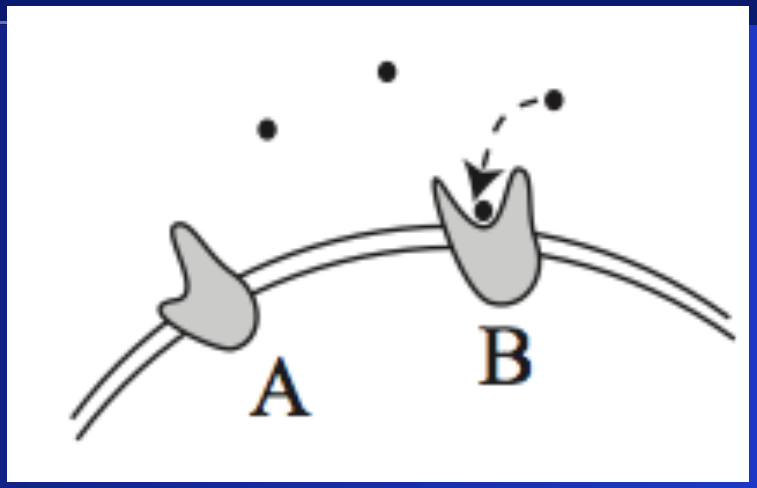
Similarly, probability of reverse transition during Δt

Prob = $k_{-1}\,\Delta t\,[1 + E(\Delta t)]$

Examples:



Closed and open membrane channels



Conformation change in a cell-surface receptor

Markov properties:

1. Transitions between states are *random*.

2. The probability that a transition occurs *does not depend on the history of previous events*

3. If the environment is constant, the transitions do not depend on the time of observation.

4. Everything is independent of space, i.e. the reaction is well-mixed.

Formulating the equation for A

decrease in A molecules

$=$ total number of A molecules $\times$ fraction that become B

$= A \cdot (k_1 \Delta t).$

$$A(t + \Delta t) - A(t) = -A(t) \cdot (k_1 \Delta t) + B(t) \cdot (k_{-1} \Delta t)$$

Continuum limit is an ODE:

Dividing by Δt, *taking the limit as* $\Delta t \to 0$

$$\frac{dA}{dt} = \lim_{\Delta t \to 0} \frac{A(t+\Delta t) - A(t)}{\Delta t},$$

$$\frac{dA}{dt} = -k_1 A + k_{-1} B.$$

Similarly,

$$\frac{dB}{dt} = k_1 A - k_{-1} B.$$

System of ODEs

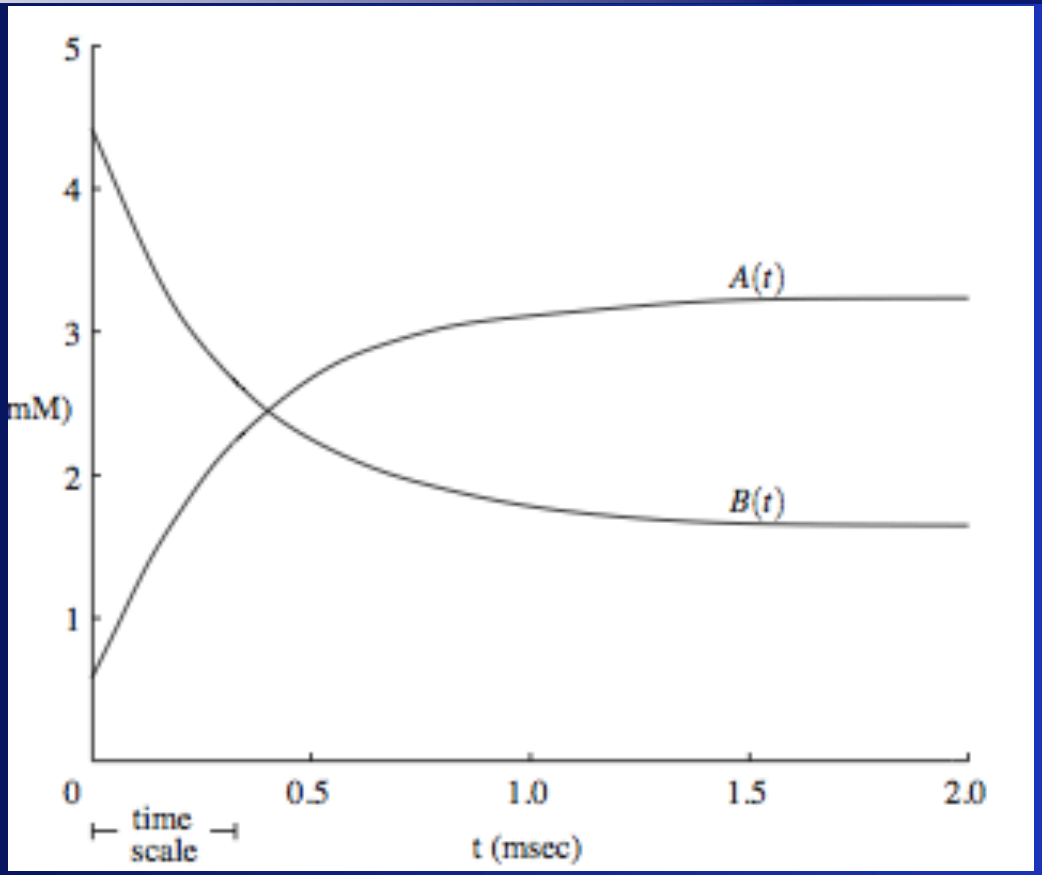
$$\frac{dA}{dt} = -k_1 A + k_{-1} B.$$

$$\frac{dB}{dt} = k_1 A - k_{-1} B\ .$$

$$A(0) = A_0,$$
$$B(0) = B_0.$$

$$A(t) + B(t) = M.$$

Solutions



Law of Mass Action

In a reaction involving the interaction of two types of molecules, the rate of reaction is proportional to the concentrations of the two reactants.

$$A + B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} P ,$$

Rate equations

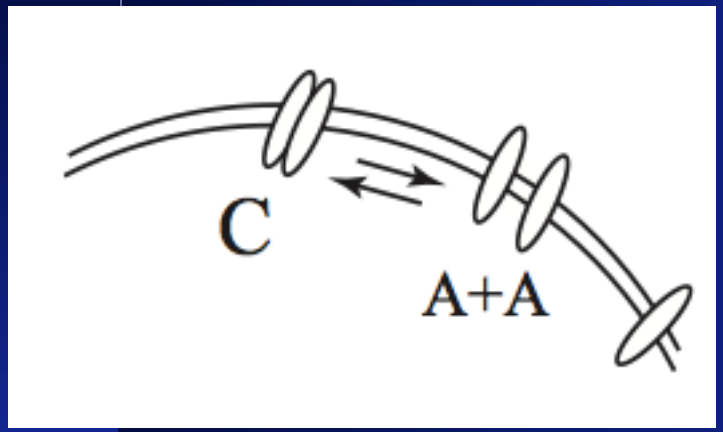
$$A + B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} P \ ,$$

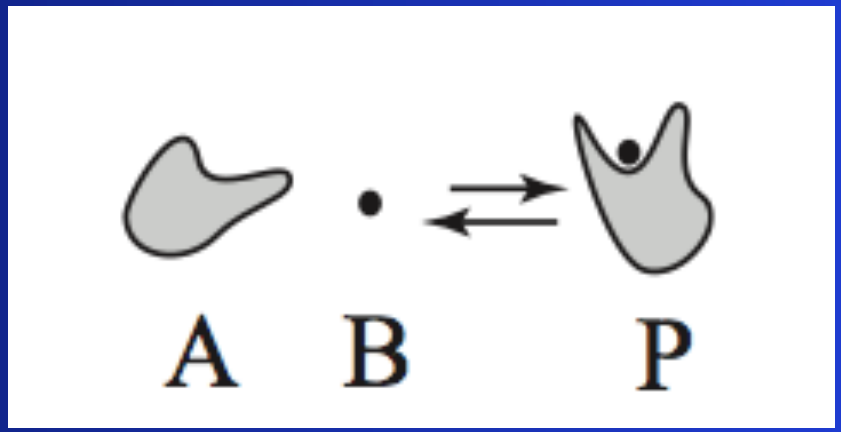
$$\frac{dA}{dt} = -k_+ AB + k_- P$$

$$\frac{dB}{dt} = -k_+ AB + k_- P$$

$$\frac{dP}{dt} = k_+ AB - k_- P$$

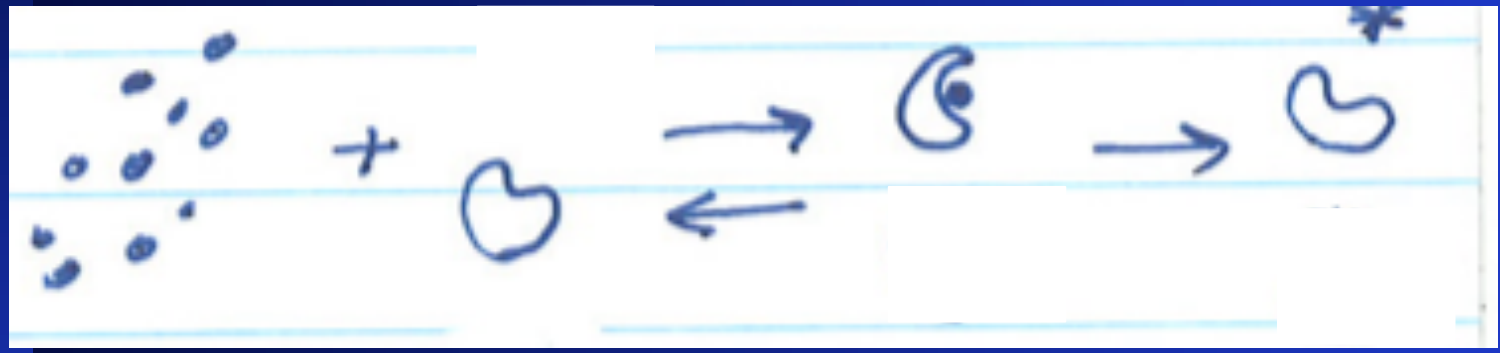
Examples





Enzyme reactions

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C \xrightarrow{k_2} E + P\,.$$



Full model equations

$$
\begin{aligned}
dE/dt &= -k_1 ES + k_{-1} C + k_2 C \,, \\
dS/dt &= -k_1 ES + k_{-1} C \,, \\
dC/dt &= k_1 ES - k_{-1} C - k_2 C \,, \\
dP/dt &= k_2 C \,.
\end{aligned}
$$

$E(0)=E0,\ \ S(0)=S0,\ \ \ C(0)=0,\ \ \ P(0)=0.$

Conservation:

$$E(t) + C(t) = E_0$$

$$S(t) + C(t) + P(t) = S_0$$

Quasi steady state

$$dC/dt \approx 0$$

$$C \approx \frac{E_0 S}{K_m + S}.$$

$$\frac{dP}{dt} = \frac{V_{\max} S}{K_m + S}.$$

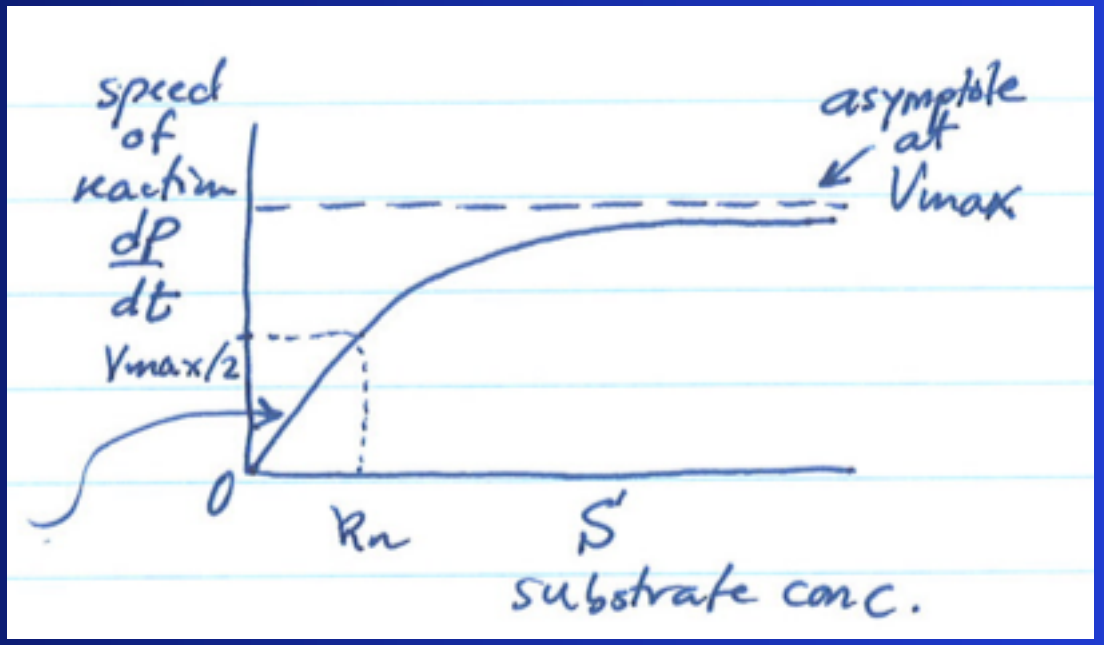
$$K_m = \frac{k_{-1} + k_2}{k_1}$$

$$V_{\max} \equiv k_2 E_0,$$

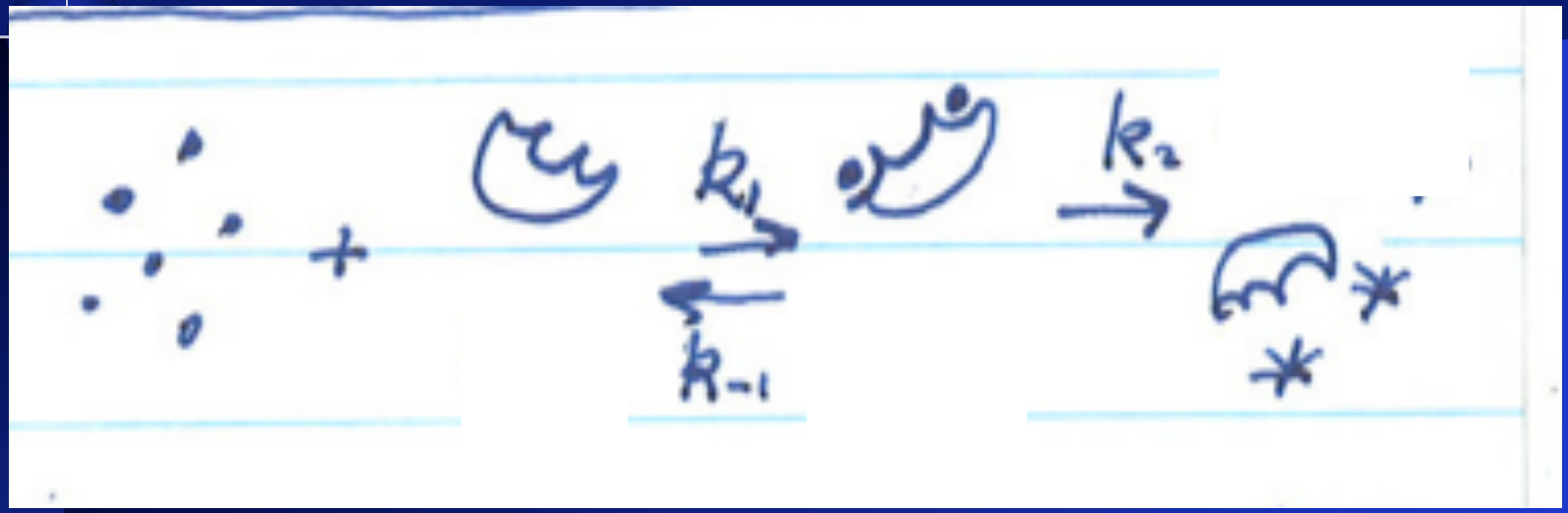
Michaelis Menten Kinetics

Speed of the reaction (V) depends on the substrate concentration as follows:

$$V = \frac{V_{max} S}{K_m + S}$$

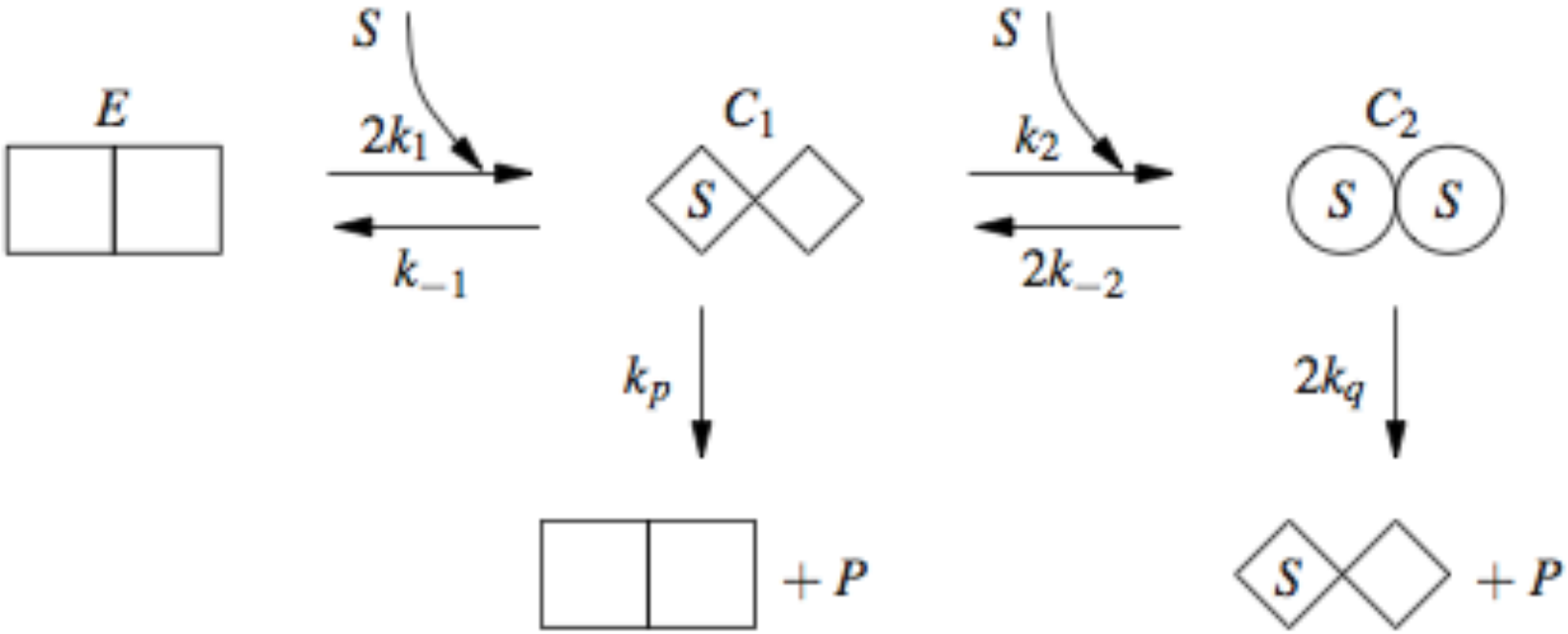


Cooperativity

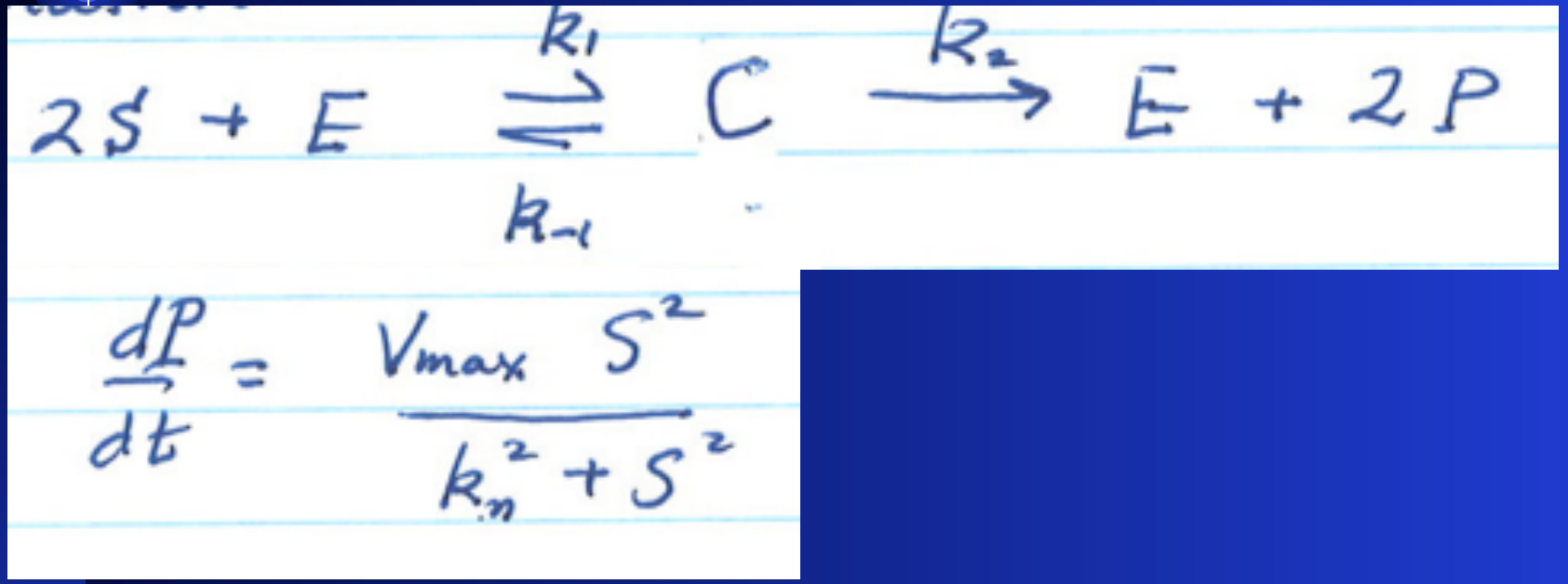


Enzymes with multiple binding sites can exhibit cooperativity: binding of one substrate molecule facilitates the binding of a second one.

Full scheme

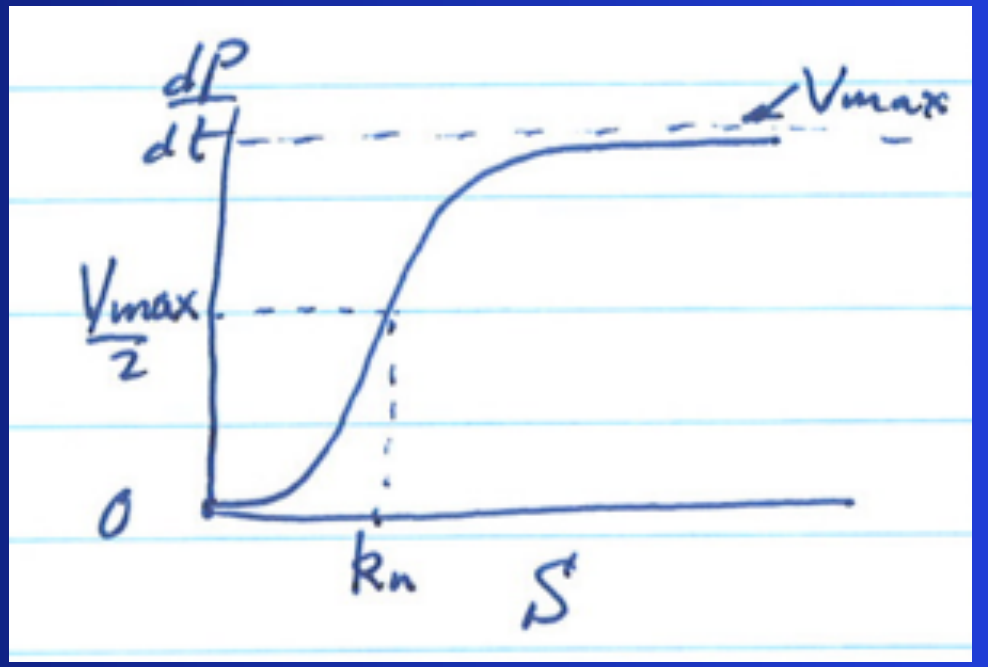


Approximate scheme



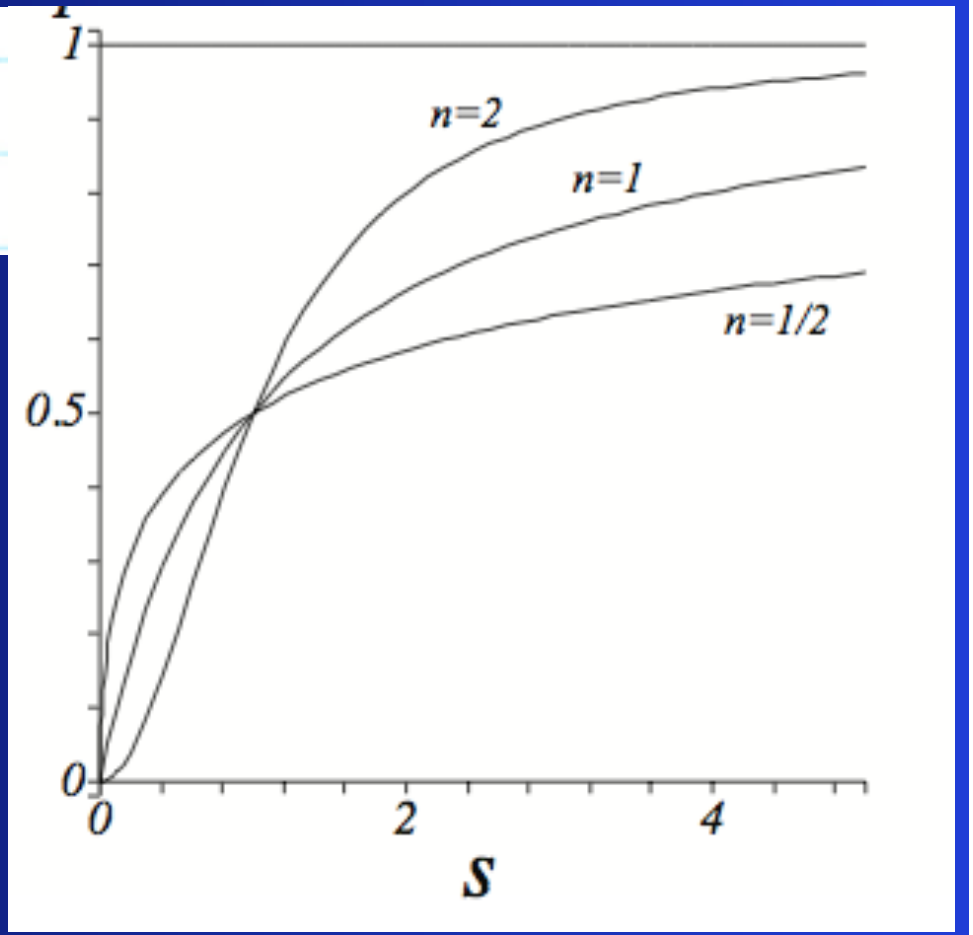
Sigmoidal kinetics

$$\frac{dP}{dt} = \frac{V_{max}\, S^2}{k_n^2 + S^2}$$



Generalization: Hill function

$$f(S) = \frac{V_{max}\, S^{n}}{k_n^{n} + S^{n}}$$



Competitive inhibition

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C_1 \xrightarrow{k_2} P_1 + E$$

$$I + E \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} C_2 \xrightarrow{k_4} P_2 + E$$

$$\text{Reaction Rate} \approx \frac{V_S \, S}{\left[S + K_m^S \left(1 + \frac{i}{K_m^i} \right) \right]}$$

$$K_m^i = \frac{k_{-3} + k_4}{k_3}$$