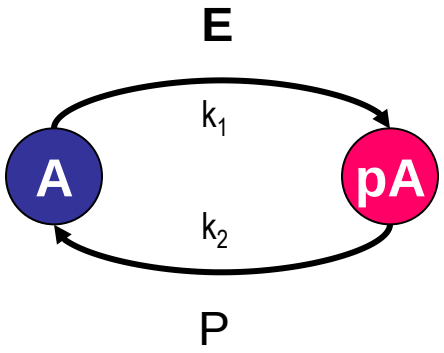


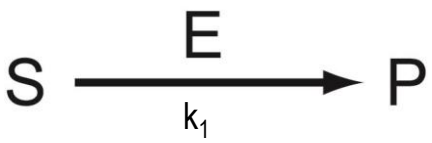
Modeling Molecular Processes-2

Enzymatic Reaction

Most of the biochemical processes involve enzymes

Rate $= k_1.[E][S]$

Simplest scheme

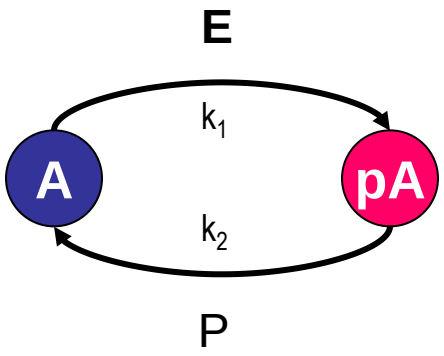


$$\frac{d[P]}{dt} = k_1.[E][S]$$

Important:
Enzyme (E) does not get used up → concentration of enzyme will not get affected by this reaction

$$\frac{d[S]}{dt} = -k_1.[E][S]$$

Two opposing reactions



Rate for forward reaction $= k_1.[E][A]$

Rate for backward reaction $= k_2[P][pA]$

$$\frac{d[pA]}{dt} = k_1.[E][A] - k_2[P][pA]$$

$$\frac{d[A]}{dt} = -k_1.[E][A] + k_2[P][pA]$$

Considering conservation, $[A]_T = [A] + [pA]$

$$\frac{d[pA]}{dt} = k_1.[E]([A]_T - [pA]) - k_2[P][pA]$$

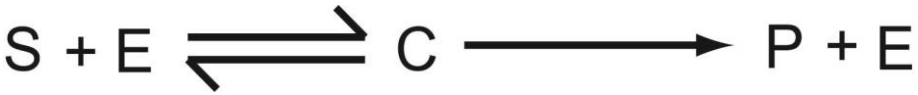
Enzymatic Reaction

Detailed scheme

Assumptions:

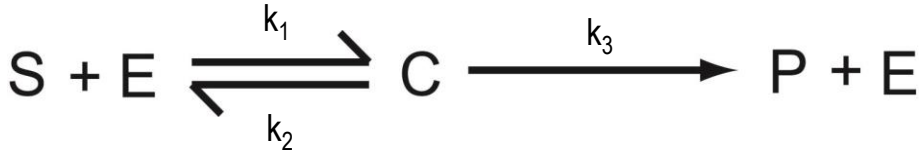
a) the inter-conversion between substrate-enzyme (S-E) and product-enzyme (P-E) complexes is very fast. Consider them as a single entity, C.

b) the product does not bind to the enzyme.



Enzymatic Reaction

Detailed scheme:



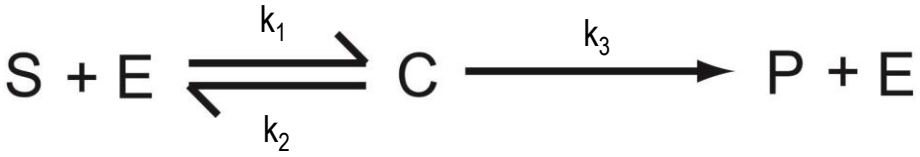
$$\frac{d[S]}{dt} = -k_1.[E][S] + k_2[C]$$

$$\frac{d[E]}{dt} = -k_1.[E][S] + k_2[C] + k_3[C]$$

$$\frac{d[C]}{dt} = k_1.[E][S] - k_2[C] - k_3[C]$$

$$\frac{d[P]}{dt} = k_3[C]$$

Enzymatic Reaction



$$\frac{d[S]}{dt} = -k_1.[E][S] + k_2[C]$$

$$\frac{d[E]}{dt} = -k_1.[E][S] + k_2[C] + k_3[C]$$

$$\frac{d[C]}{dt} = k_1.[E][S] - k_2[C] - k_3[C]$$

$$\frac{d[P]}{dt} = k_3[C]$$

Conservation of enzyme: $[E]_T = [E] + [C]$

Assumptions to simplify:

a) [S] >> [E]

b) the complex, C, remains in quasi-steady state

$$\frac{d[C]}{dt} = k_1.[E][S] - k_2[C] - k_3[C] = 0$$

$$\Rightarrow k_1.[E][S] - (k_2 + k_3)[C] = 0$$

$$\Rightarrow k_1.([E]_T - [C]).[S] - (k_2 + k_3)[C] = 0$$

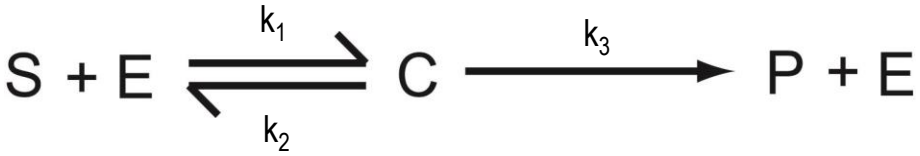
$$\Rightarrow k_1.([E]_T - [C]).[S] = (k_2 + k_3)[C]$$

$$\Rightarrow ([E]_T - [C]).[S] = \frac{(k_2 + k_3)}{k_1}[C]$$

$$\Rightarrow [E]_T[S] = \frac{(k_2 + k_3)}{k_1}[C] + [C][S]$$

$$\Rightarrow [C] = \frac{[E]_T[S]}{\frac{(k_2 + k_3)}{k_1} + [S]}$$

Enzymatic Reaction



$$\frac{d[S]}{dt} = -k_1.[E][S] + k_2[C]$$

$$\frac{d[E]}{dt} = -k_1.[E][S] + k_2[C] + k_3[C]$$

$$\frac{d[C]}{dt} = k_1.[E][S] - k_2[C] - k_3[C]$$

$$\frac{d[P]}{dt} = k_3[C]$$

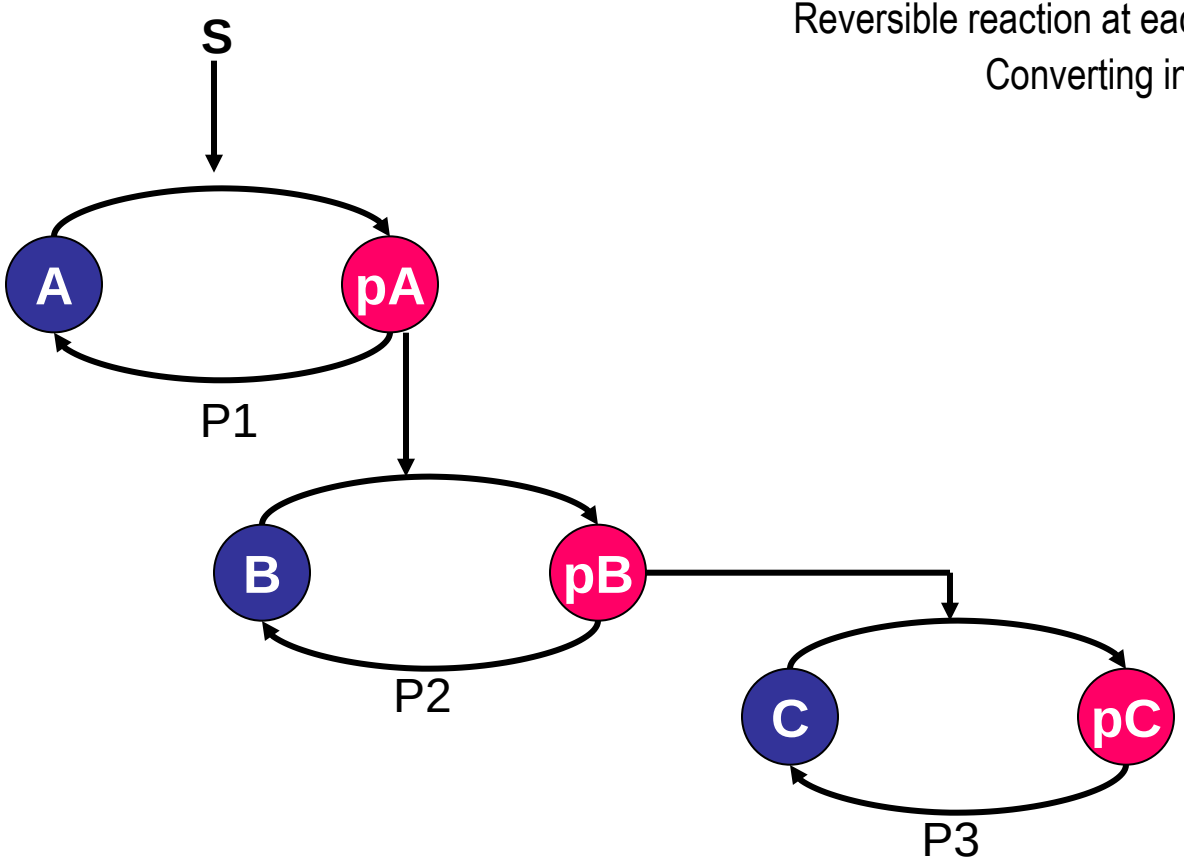
$$[C] = \frac{[E]_T[S]}{\frac{(k_2 + k_3)}{k_1} + [S]}$$

$$\frac{d[P]}{dt} = k_3[C] = k_3 \cdot \frac{[E]_T[S]}{\frac{(k_2 + k_3)}{k_1} + [S]}$$

Define: $K_M = \frac{(k_2 + k_3)}{k_1}$

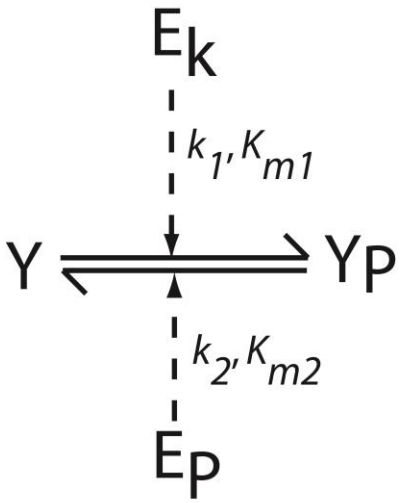
$$\frac{d[P]}{dt} = \frac{k_3[E]_T[S]}{K_M + [S]}$$: Michaelis–Menten kinetics

Enzymatic Cascade



Reversible reaction at each step, works as switches:
Converting input dynamics to output dynamics

Enzymatic Switch



Both forward and reversible reaction follows Michaelis–Menten kinetics

$$\text{Rate of forward reaction} = \frac{k_1.[E_k].[Y]}{K_{m1}+[Y]}$$

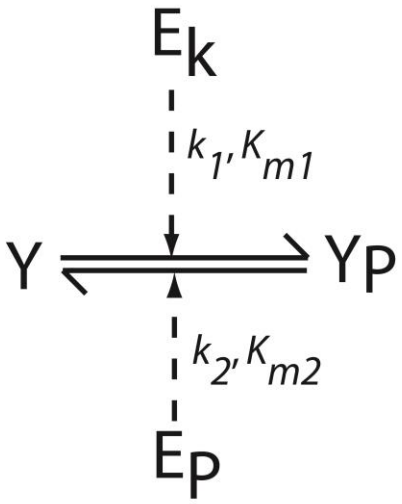
$$\text{Rate of reverse reaction} = \frac{k_2.[E_p].[Yp]}{K_{m2}+[Yp]}$$

$$\frac{d[Yp]}{dt} = \frac{k_1.[E_k].[Y]}{K_{m1}+[Y]} - \frac{k_2.[E_p].[Yp]}{K_{m2}+[Yp]}$$

$$[Y]_T = [Y]+[Yp]$$

$$\frac{dYp}{dt} = \frac{k_1.[E_k].([Y]_T-[Yp])}{K_{m1}+([Y]_T-[Yp])} - \frac{k_2.[E_p].[Yp]}{K_{m2}+[Yp]}$$

Enzymatic Switch



Both forward and reversible reaction follows Michaelis–Menten kinetics

$$\frac{dYp}{dt} = \frac{k_1.[E_k].([Y]_T - [Yp])}{K_{m1} + ([Y]_T - [Yp])} - \frac{k_2.[E_p].[Yp]}{K_{m2} + [Yp]}$$

At steady state:

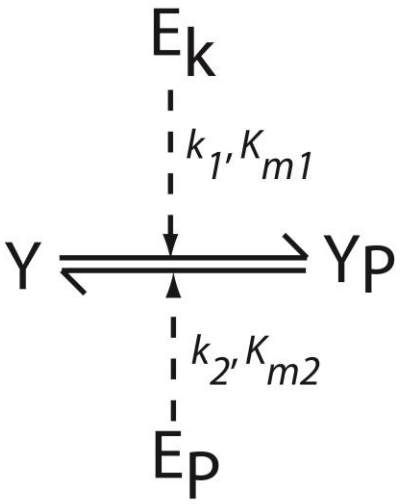
$$\frac{dYp}{dt} = \frac{k_1.[E_k].([Y]_T - [Yp])}{K_{m1} + ([Y]_T - [Yp])} - \frac{k_2.[E_p].[Yp]}{K_{m2} + [Yp]} = 0$$

On algebraic rearrangement

$$[E_k] = \frac{1}{k_1} . \frac{v_2 . \frac{[Yp]}{[Y]_T}}{J_2 + \frac{[Yp]}{[Y]_T}} . \frac{J_1 + (1 - \frac{[Yp]}{[Y]_T})}{(1 - \frac{[Yp]}{[Y]_T})}$$

Here, $v_2 = k_2.E_p$ $J_1 = \frac{K_{m1}}{Y_T}$ $J_2 = \frac{K_{m2}}{Y_T}$

Enzymatic Switch



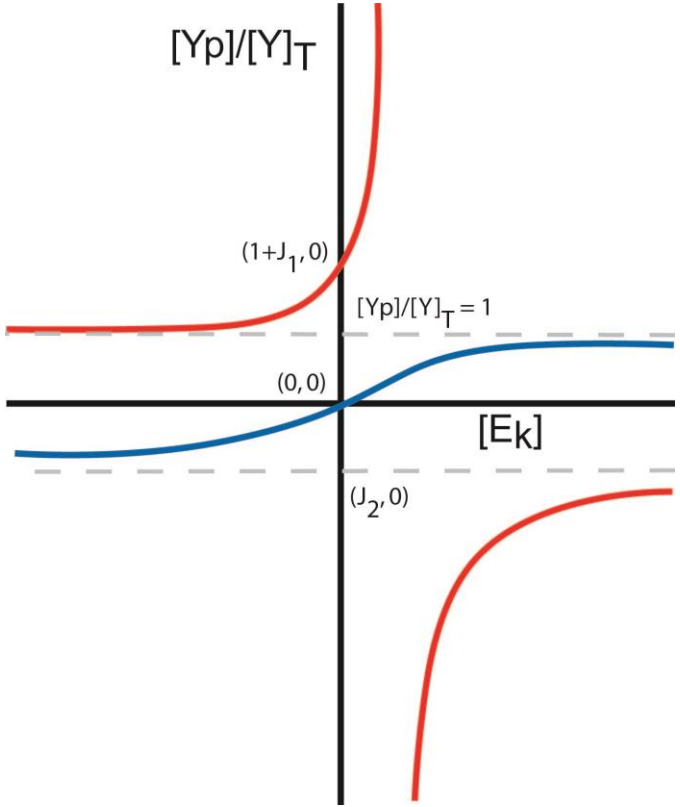
Both forward and reversible reaction follows Michaelis–Menten kinetics

At steady state:

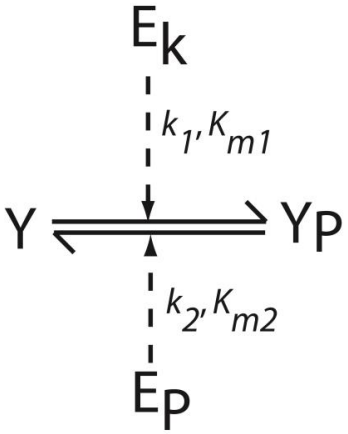
$$[E_k] = \frac{1}{k_1} \cdot \frac{v_2 \cdot \frac{[Yp]}{[Y]_T}}{J_2 + \frac{[Yp]}{[Y]_T}} \cdot \frac{J_1 + (1 - \frac{[Yp]}{[Y]_T})}{(1 - \frac{[Yp]}{[Y]_T})}$$

Here, $v_2 = k_2 . E_p$ $\quad J_1 = \frac{K_{m1}}{Y_T}$

$$J_2 = \frac{K_{m2}}{Y_T}$$

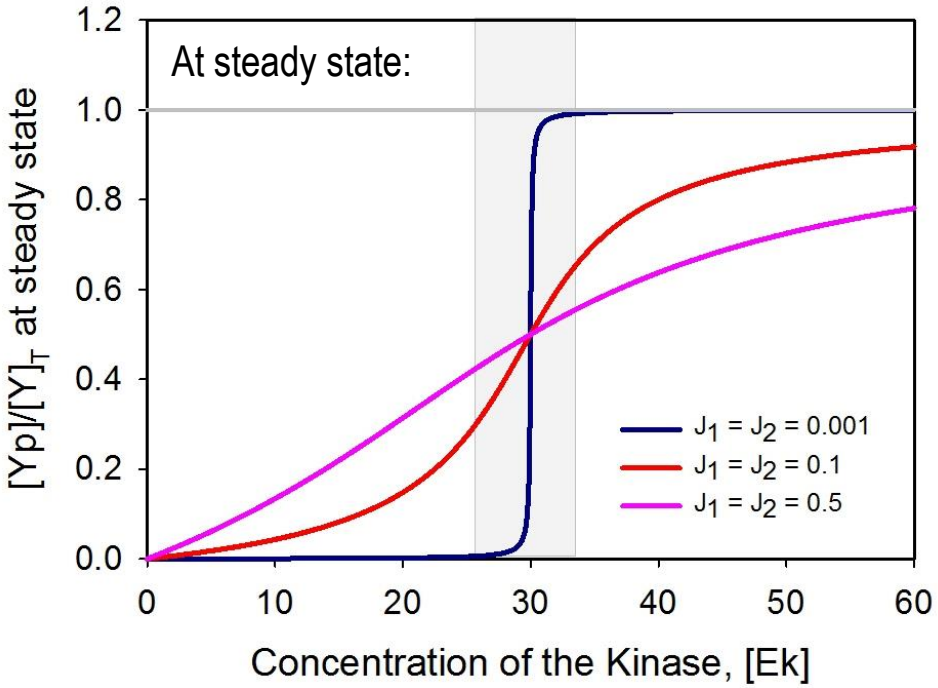


Enzymatic Switch



Both forward and reversible reaction follows Michaelis–Menten kinetics

$$J_1 = \frac{K_{m1}}{Y_T} \qquad J_2 = \frac{K_{m2}}{Y_T}$$



Rheostat: when $0 < J_1, J_2 < 1$

Ultra-sensitive ON-OFF switch: when $0 < J_1, J_2 \ll 1$

Key points:

1. An enzymatic reaction can be modeled using Law of Mass action without considering any mechanistic aspects.
2. We can consider Michaelis–Menten kinetics when substrate concentration is much higher than enzyme and substrate-enzyme complex remains at quasi-steady state.
3. A reversible enzymatic reaction, following Michaelis–Menten kinetics can work like a swtich:
   a) A rheostat when concentration of the substrate is close to Michaelis–Menten constants
   b) An ultra-sensitive ON-OFF switch when concentration of the substrate is much higher than Michaelis–Menten constants