The Michaelis-Menten model of catalysis by enzymes

The standard way to model enzymes is with the Michaelis-Menten equation

In this model, an enzyme catalyses the *irreversible* conversion of substrate *S* to product *P*

$$\mathrm{E} + \mathrm{S} \underset{b}{\overset{f}{\rightleftharpoons}} \mathrm{C} \xrightarrow{k} \mathrm{P} + \mathrm{E}$$

Using the law of mass action

$$\begin{aligned}
\frac{d[E]}{dt} &= -f[E][S] + (b+k)[C] \\
\frac{d[S]}{dt} &= -f[E][S] + b[C] \\
\frac{d[C]}{dt} &= f[E][S] - (b+k)[C] \\
\frac{d[P]}{dt} &= k[C].
\end{aligned}$$

We can simplify the equations because the reaction conserves enzymes

$$\mathrm{E} + \mathrm{S} \underset{b}{\overset{f}{\rightleftharpoons}} \mathrm{C} \xrightarrow{k} \mathrm{P} + \mathrm{E}$$

$$\begin{aligned}
\frac{d[E]}{dt} &= -f[E][S] + (b+k)[C] \\
\frac{d[S]}{dt} &= -f[E][S] + b[C] \\
\frac{d[C]}{dt} &= f[E][S] - (b+k)[C] \\
\frac{d[P]}{dt} &= k[C].
\end{aligned}$$

implying

$$\frac{d[E]}{dt} + \frac{d[C]}{dt} = 0$$

and so

$$[E] + [C] = [E]_0 + [C]_0 = E_{\mathrm{tot}}$$

the amount of enzyme is conserved

Most of the enzyme is bound up with substrate because there so much more substrate compared to enzyme

quasi-steady state

$$\frac{d[C]}{dt} \simeq 0$$

because the amount of enzyme is conserved

but

$$\frac{d[C]}{dt} = f[E][S] - (b+k)[C]$$

and so

$$f[E][S] = (b+k)[C]$$

at quasi-steady state

Using

$$[E] = E_{\text{tot}} - [C]$$

we have

$$[C] \simeq \frac{E_{\text{tot}}[S]}{\frac{b+k}{f} + [S]}$$

at quasi-steady state

The Michaelis-Menten equation describes the rate of formation of the product, or equally the rate of consumption of the substrate

$$\frac{d[P]}{dt} = k[C] \qquad \text{or} \qquad \frac{d[P]}{dt} \simeq \frac{kE_{\text{tot}}[S]}{\frac{b+k}{f} + [S]} \qquad \text{at quasi-steady state}$$

$$\mathrm{E} + \mathrm{S} \underset{b}{\overset{f}{\rightleftharpoons}} \mathrm{C} \xrightarrow{k} \mathrm{P} + \mathrm{E}$$

which is usually written as

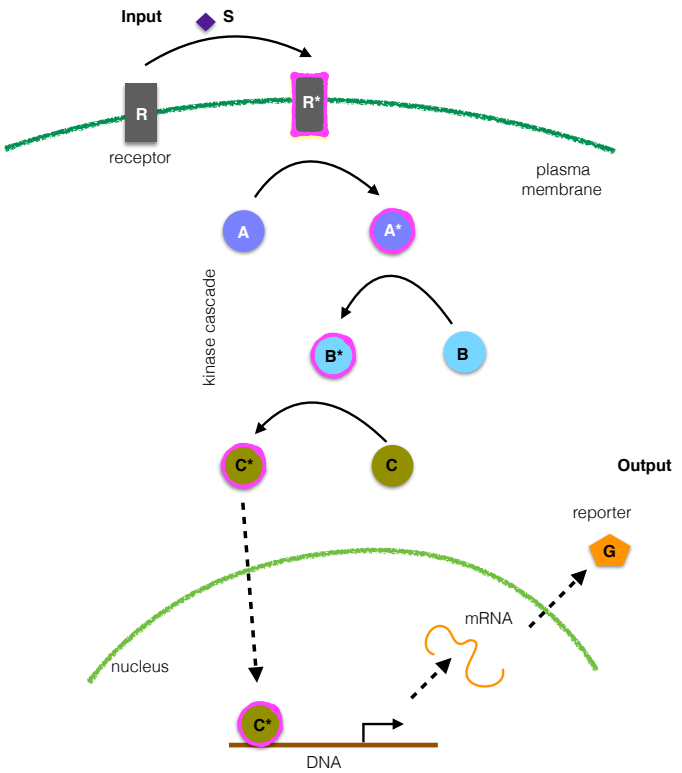
$$\boxed{\frac{d[P]}{dt} \simeq \frac{V_{\max}[S]}{K_m + [S]}}$$

with $\quad V_{\max} = kE_{\text{tot}} \quad ; \quad K_m = \frac{b+k}{f}$

A more formal analysis shows that the assumption of quasi-steady state requires

$$\frac{E_{\text{tot}}}{[S]_0 + K_m} \ll 1$$

Modelling signal transduction IV.i



phosphorylation

$$\mathrm{A}^* + \mathrm{B} \underset{b_B}{\overset{f_B}{\rightleftharpoons}} \mathrm{C}_{\mathrm{AB}} \xrightarrow{k_B} \mathrm{B}^* + \mathrm{A}^* \quad \text{(enzyme)}$$

The rate of change of *[B*]* has a positive term

$$\frac{k_B[A^*][B]}{\frac{b_B+k_B}{f_B}+[B]}$$

de-phosphorylation

$$\mathrm{B}^* + \mathrm{P} \underset{b'_B}{\overset{f'_B}{\rightleftharpoons}} \mathrm{C}_{\mathrm{PB}} \xrightarrow{k'_B} \mathrm{B} + \mathrm{P} \quad \text{(enzyme)}$$

The rate of change of *[B*]* has a negative term

$$-\frac{k'_B[P][B^*]}{\frac{b'_B+k'_B}{f'_B}+[B^*]}$$

The rate equation for *[B*]*

$$\frac{d[B^*]}{dt} \simeq \frac{k_B[A^*][B]}{\frac{b_B+k_B}{f_B}+[B]} - \frac{k'_B[P][B^*]}{\frac{b'_B+k'_B}{f'_B}+[B^*]}$$

Modelling signal transduction IV.ii

We will simplify the rate equation for *[B*]*

$$\frac{d[B^*]}{dt} \simeq \frac{k_B[A^*](B_0 - [B^*])}{\frac{b_B+k_B}{f_B} + B_0 - [B^*]} - \frac{k'_B[P][B^*]}{\frac{b'_B+k'_B}{f'_B} + [B^*]} \qquad \text{because} \qquad B_0 = [B] + [B^*].$$

by assuming that the phosphatase is far from being saturated

$$[B^*] \ll \frac{b'_B+k'_B}{f'_B}$$

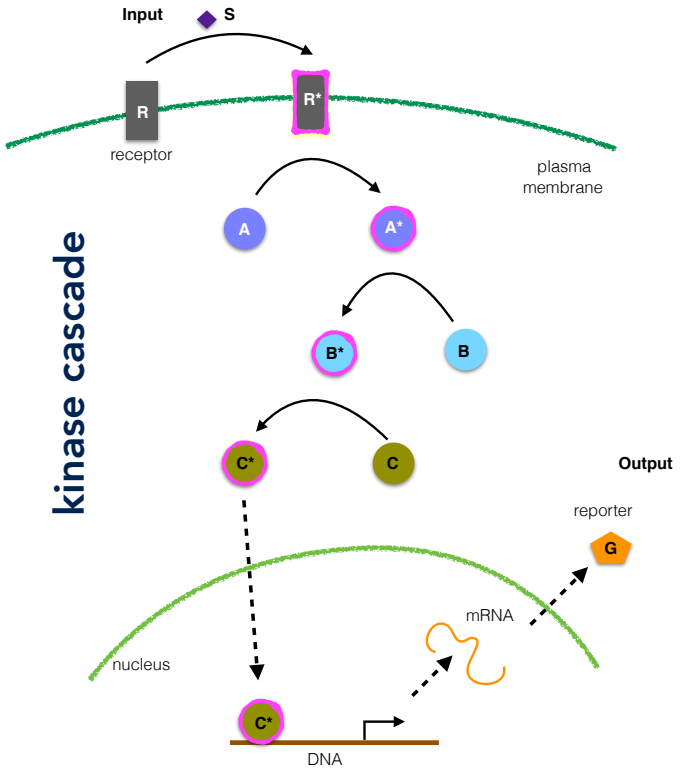
so that

$$\frac{d[B^*]}{dt} \simeq \frac{k_B[A^*](B_0 - [B^*])}{\frac{b_B+k_B}{f_B} + B_0 - [B^*]} - d_B[B^*]$$

with

$$d_B = \frac{f'_B k'_B[P]}{b'_B + k'_B}$$

Modelling signal transduction IV.iii



We have a complete model for the cytoplasmic part of the signal transduction

allosteric receptor

phosphatase far from saturation

kinase cascade

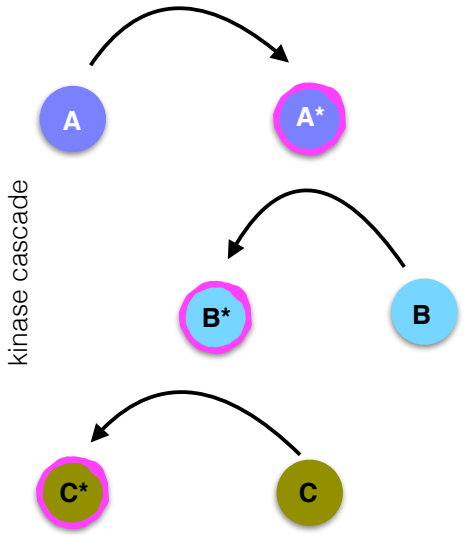
$$\frac{d[A^*]}{dt} = \frac{k_A R_0(1+K^*[S])}{1+K^*[S]+L(1+K[S])}(A_0-[A^*]) - d_A[A^*]$$

$$\frac{d[B^*]}{dt} = \frac{k_B[A^*](B_0-[B^*])}{\frac{b_B+k_B}{f_B}+B_0-[B^*]} - d_B[B^*]$$

$$\frac{d[C^*]}{dt} = \frac{k_C[B^*](C_0-[C^*])}{\frac{b_C+k_C}{f_C}+C_0-[C^*]} - d_C[C^*]$$

Enzymatic cascades

Why have a cascade of kinases? Enzymatic cascades can increase ultrasensitivity



Active *B* is a Hill function of active *A*

$$[B^*] = [B^*]_{\max} \cdot \frac{[A^*]^{n_B}}{K_B^{n_B} + [A^*]^{n_B}}$$

steady state

Active *C* is a Hill function of active *B*

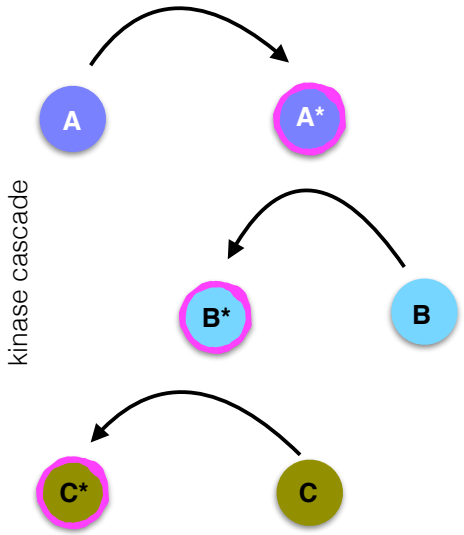
$$[C^*] = [C^*]_{\max} \cdot \frac{[B^*]^{n_C}}{K_C^{n_C} + [B^*]^{n_C}}$$

How does active *C* depend on active *A*?

$$[C^*] = [C^*]_{\max} \cdot \frac{\left([B^*]_{\max} \frac{[A^*]^{n_B}}{K_B^{n_B} + [A^*]^{n_B}}\right)^{n_C}}{K^{n_C} + \left([B^*]_{\max} \frac{[A^*]^{n_B}}{K_B^{n_B} + [A^*]^{n_B}}\right)^{n_C}}$$

can we make this function approximate a Hill function?

Hill numbers multiply in a cascade: $n_{\text{final}} = n_B\, n_C$



Active *B* is a Hill function of active *A*

$$[B^*] = [B^*]_{\max} \cdot \frac{[A^*]^{n_B}}{K_B^{n_B} + [A^*]^{n_B}}$$

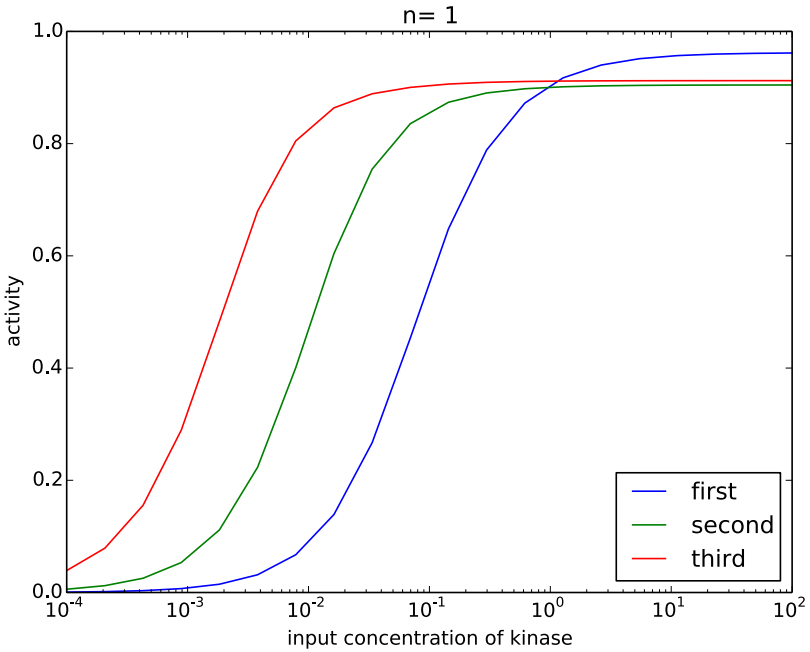
Active *C* is a Hill function of active *B*

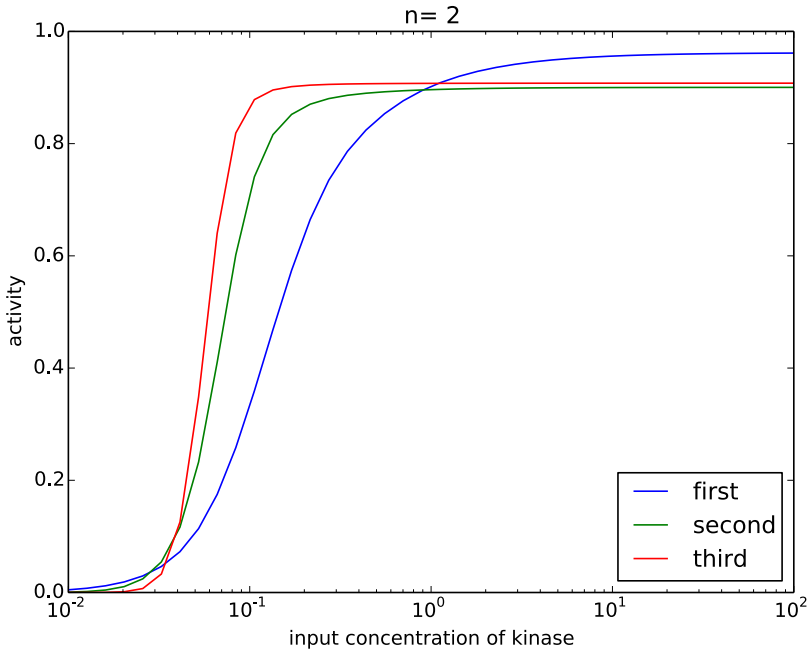
$$[C^*] = [C^*]_{\max} \cdot \frac{[B^*]^{n_C}}{K_C^{n_C} + [B^*]^{n_C}}$$

How does active *C* depend on active *A*?

$$[C^*] \simeq [C^*]_{\max} \cdot \frac{[A^*]^{n_B n_C}}{\frac{K_B^{n_B n_C} K_C^{n_C}}{[B^*]_{\max}^{n_C}} + [A^*]^{n_B n_C}} \qquad \text{if} \qquad [A^*] \ll K_B$$

For the cascade to increase sensitivity, the Hill numbers of intermediate steps must be greater than one





Many kinases require two phosphorylation to activate and so have a Hill number greater than one if the activating enzyme is distributive.

A **distributive** kinase binds, phosphorylates, dissociates, and then binds and phosphorylates again. A **processive** enzyme binds once, phosphorylates twice, and then dissociates.