The Michaelis-Menten model of catalysis by enzymes



form *P* (phosphorylated *S*). Using the law of mass action, the rate equation using the law of mass action

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



Catalysis does not use up the enzyme, and we see that implying

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

and so

$$
[E] + [C] = [E]_0 + [C]_0 = E_{\text{tot}}
$$
 of enzyme is

the amount time (although [*S*] and [*P*] do), at least while levels of *S* remain suciently high. We say that where the right-hand side is the total amount of enzyme initially present ( $\frac{1}{\sqrt{2}}$ is a conserved in the total amount of substrate is conserved in its various forms (either as free  $\sim$ conserved where the right-hand side is the right-hand side is the total amount of enzyme initially present, which I denote as

Most of the enzyme is bound up with substrate because there so much more substrate compared to enzyme *dt* = 0 (2.63)

quasi-steady state

\n
$$
\frac{d[C]}{dt} \simeq 0
$$
\nbecause the amount of  
enzyme is conserved

 $dt$   $\qquad$   $\qquad$ 

but  $\mathsf{b}$ ut  $E$  **E**tot. Similarly, substrate is converted into product and no new substrate is converted in the so that  $E$ 

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

and so (*d*[*S*]*/dt <* 0 and *d*[*P*]*/dt >* 0). If *d*[*C*]*/dt* ' 0, then enzyme, which is often true initially, so that almost all the enzyme is bound up in complex with  $t_{\rm dH}$  substrate most of time. The concentration of the concentration of the complex does not then change with  $\alpha$ 

$$
f[E][S] = (b+k)[C] \qquad \qquad \text{at quasi-steady state}
$$

 $f_{\rm 2.6}$  Using  $f_{\rm 2.6}$ (*d*[*S*]*/dt <* 0 and *d*[*P*]*/dt >* 0). If *d*[*C*]*/dt* ' 0, then

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

we have  $f(x)$  we have  $\frac{1}{2}$ .62. Combining Eqs 2.65 with Eqs 2.65 with Eqs 2.65 with Eqs 2.64, we can show that Eqs 2.

$$
[C] \simeq \frac{E_{\text{tot}}[S]}{\frac{b+k}{f} + [S]}
$$
 at quasi-steady state



we have the Michaelis-Menten equation:

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

for the initial rate of an entity  $\mathbf{v} = \mathbf{v} \cdot \mathbf{v} = \mathbf{v} \cdot \mathbf{v}$  $\mathbf{v}_{\text{max}} - \kappa L_{\text{tot}}$ ,  $\mathbf{v}_{\text{max}} - f$  $\mathbf{b}$  is the total and the total and the total and  $\mathbf{b}$  and  $\mathbf{b}$  is  $\mathbf{b}$  is various forms  $\mathbf{b}$  in  $\mathbf{b}$  is various forms  $\mathbf{b}$  in  $\mathbf{b}$  is various forms  $\mathbf{b}$  in  $\mathbf{b}$  is various forms  $\$ with  $v_{\text{max}} - w_{\text{tot}}$ ,  $v_{\text{max}} - w_{\text{tot}}$ with  $V_{\text{max}} = kE_{\text{tot}}$  ;  $K_m = \frac{b+k}{f}$ reaction occurs at half this rate is given by the Michaelis constant, *Km*. with  $\frac{+ \kappa}{f}$ 

A more formal analysis shows that the assumption of quas time (although [*S*] and [*P*] do), at least while levels of *S* remain suciently high. We say that [*C*] is at quasi-steady-state because *d*[*C*]*/dt* ' 0, but the system as a whole is not at steady-state 19 *d*[*P*] l analysis sho<mark>v</mark> A more formal analysis shows that the assumption of quasi-steady state  $\cdot$ for the initial rate of an enzymatic reaction. The maximum rate of the reaction is given by *V*max The Michaelis-Menten equation is approximately show that the more careful analysis shows that the more careful

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

## Modelling signal transduction IV.i matically, but the technique will include the technique techniques by developing  $\mathbb N$  of a model of a signal Modelling signal transduction IV.i  $\Box$  and  $\Box$  and  $\Box$  the activation of the activation of the receptors in Fig. 1 (Eq. 2.59), we can consider the receptors in Fig. 1 (Eq. 2.59), we can consider the receptors in Fig. 1 (Eq. 2.59), we can consider the re



 *<sup>k</sup>*<sup>0</sup> *b*0 *B*+*k*<sup>0</sup> *B f*0 *B* + [*B*⇤] The rate equation for *[B\*]*

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

## **Phosphorylation** obeys Michaelis-Menten kinetics: Michaelis-Menten kinetics: Michaelis-Menten kinetics: Michaelis-Menten kinetics: Michaelis-Menten kinetics: Michaelis-Menten kinase *B*, which is propagated with its propa activated by *A*⇤. We will assume that this activation obeys Michaelis-Menten kinetics:  $\mathsf{proport}$  model of the activation of the activation of the receptors in  $\mathsf{proport}$

$$
A^* + B \xrightarrow[b_B]{f_B} C_{AB} \xrightarrow{k_B} B^* + A^*
$$

The rate of change of *[B\*]* has a positive term *kB*[*A*⇤][*B*] *h*  $k_B[A^*][B]$ The rate of change of [*B* ] is thange of *b<sup>B</sup> B\*l* has a POSITIVE CONTROLS **TEATED** 

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

$$
\textbf{de-phosphorylation}
$$
\n
$$
B^* + P \xleftarrow{\frac{f'_B}{b'_B}} C_{PB} \xrightarrow{k'_B} B + P
$$

of change of<br><sup>:erm</sup> *b*0 *B*+*k*<sup>0</sup> negative term in the rate of  $k^{\prime}$  [*B* [*B*∗] *.* (2.72) *B*<sup> $\bullet$ </sup> and so a help rate of change of *[B\*]* has a *.* (2.72) *. .*  $\frac{1}{2}$ 

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

## Modelling signal transduction IV.ii *f*0 *B* + [*B*⇤] Hence *d*[*B*⇤] *dt* ' and so a negative term in the rate of change of [*B*⇤] of *<sup>B</sup>*[*P*][*B*⇤] *l* transdi **B**  $\frac{1}{2}$  **B**  $\frac{1}{2}$

We will simplify the rate equation for *[B\*]*  $a$ rate equation fo *bB*+*k<sup>B</sup> <sup>f</sup><sup>B</sup>* + [*B*] *<i>b*+*b*<sup>+</sup>*k*<sup>0</sup> .<br>niv  $\overline{D}$ n to *kB*[*A*⇤](*B*<sup>0</sup> [*B*⇤])  $f(x + b)$ equation fo

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

by assuming that the phosphatase is far from being saturated *f*0  $\frac{1}{2}$ ic fa  $s$  far from being satura by assuming that the phosphatase is far from being saturated + *B*<sup>0</sup> [*B*⇤]  $a$ ssuming that *<sup>k</sup>*<sup>0</sup> *b*0 *B*+*k*<sup>0</sup> *B* phosphatase is far from being sa<sup>.</sup> *kB*[*A*⇤](*B*<sup>0</sup> [*B*⇤])

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

 $\overline{b}$  so that *bB*+*k<sup>B</sup>* so that aso that enzyme *P* works far from saturation is made so that  $\mathbb{R}$  both  $\mathbb$ 

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

with

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

## Modelling signal transduction IV.iii matical material induction will include the technique techniques by  $\mu$ pathway (Fig. 19). Pathway to the electron feed-



Enzymatic cascades

Why have a cascade of kinases? Enzymatic cascades can increase ultrasensitivity in turn activates the third and so on – have the potential to generate response curves that are Why have a cascade of kinases? Enzymatic cascades can increase of oocytes in the frog *Xenopus laevis*. The hormone progesterone activates the MAP kinase in turn activates the third and so on – have the potential to generate response curves that are



Active B is a Hill function of active A in turn activates the third and so on – have the potential to generate response curves that are example in a well understood a well in the MAC tive  $B$  is a Hill function of active  $A$ 

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

[*C*⇤ ]=[*C*⇤ Active C is a Hill function of active *B*  $A \cdot \text{triv} \circ C$  is a Hill function of  $B$ stive  $B$ stead is a signoment of  $\overline{C}$  is a signoment of  $\overline{C}$  $\lambda$ *Active C* 

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

 $\overline{C}$ ]=[*C*⇤ How does active *C* depend on active *A*? ]max *·* [*B*⇤] *K<sup>n</sup><sup>C</sup>*  $\overline{\phantom{a}}$ 

$$
[C^*] = [C^*]_{\text{max}} \cdot \frac{\left([B^*]_{\text{max}} \frac{[A^*]^n B}{K_B^{n_B} + [A^*]^n B}\right)^{n_C}}{K^{n_C} + \left([B^*]_{\text{max}} \frac{[A^*]^n B}{K_B^{n_B} + [A^*]^n B}\right)^{n_C}}
$$
 can we make  
function app a Hill function

*can* we make this  $\frac{1}{\sqrt{n_C}}$  function approximate a Hill function?

Hill numbers multiply in a cascade: *n*final*= n*<sup>B</sup> *n*<sup>C</sup> ultrasensitive. A well understood example involved involves the MAP kinases involved in the maturation of  $\alpha$ of our operator of oocytes in the frog *Xenopus later in the hormone progester active* activates the Ma<sub>P</sub> kinase  $E$  , where the first enzyme in the first enzyme in the case  $\alpha$  case  $\alpha$  and the second and the se nuitiply in a cascade:  $n_{\mathsf{final}}$  =  $n_{\mathsf{B}}$   $n_{\mathsf{C}}$  $Lill$  pumbers multiply in a sassado:  $R_1 = R_1 R_2$ kin hampers malepty in a cascade. Thing the original in turn activates the third and so on – have the potential to generate response curves that are multiply in a cascade:  $n_{\text{final}} = n_{\text{B}} n_{\text{C}}$ 



Active B is a Hill function of active A  $I = \frac{1}{2}$  . If the case of the case is ultrasensitive, then each subsequent step increases the ultra-

 $u_{\rm eff}$ ultrasensitive. A well understood example involves the MAP kinases involved in the maturation in the maturation

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

Active C is a Hill function of active *B*  $A \cdot \text{triv} \circ C$  is a Hill function of  $B$ stive  $B$ steady-state *C* is a Hill function of active *<sup>C</sup>* + [*B*⇤] steady-state **and** *F C* is a Hill function of  $\overline{B}$ 

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

 $\overline{C}$ ]=[*C*⇤ How does active *C* depend on active *A*?  $\Omega$  -  $\Omega$  $\ddot{\phantom{}}$ ]=[*C*⇤

$$
[C^*] \simeq [C^*]_{\max} \cdot \frac{[A^*]^{n_{Bnc}}_{\substack{R_B^{n}C_{K_C^{n}C}\\[B^*]_{\max}^{n_C}}} + [A^*]^{n_{Bnc}}}{[A^*] \ll K_B}
$$
if  $[A^*] \ll K_B$ 

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.

 $\bigwedge$  distributive kinese binds, phosphonulates dissociates and In chemicality (*in the castally prosphery* also elected) circle<br>then binds and phosphorylates again. A **processive** enzyme binds once, phosphorylates twice, and then dissociates. How could each element of the cascade have a Hill number greater than one? If a kinase A **distributive** kinase binds, phosphorylates, dissociates, and