Computational
&
Systems Biology

Kinetic Modeling

Yazdan Asgari
2019

Kinetic Modeling - Principles

Writing the rate equations.

In general, we can write

$$X_1 \xrightarrow{v_1} X_2 \xrightarrow{v_2} X_3$$

$$\frac{\mathrm{d}X_2}{\mathrm{d}t} = v_1 - v_2$$

where v_1 and v_2 depend on the chemical kinetics of the reaction.

Principles (Mass action Law)

$$X_1 + A \xrightarrow{v_1} X_2 \xrightarrow{v_2} X_3$$

$$\frac{\mathrm{d}X_2}{\mathrm{d}t} = \underbrace{k_1 X_1 A}_{v_1} - \underbrace{k_2 X_2}_{v_2}$$

- v_i could be written in many different ways based on a reaction mechanism.
- The simplest way is using mass action rate laws (the upper example)

Theoretical foundations: *Mass Action Law*

RATE IS PROPORTIONAL TO CONCENTRATION(S)

MONOMOLECULAR REACTIONS

A ⟶ products

rate is proportional to **[A]**

$$-\frac{d[A]}{dt} = k[A]$$

monomolecular rate constant
1 / time

BIMOLECULAR REACTIONS

A + B ⟶ products

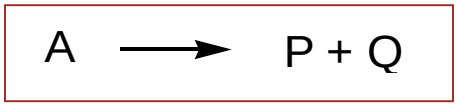
rate is proportional to **[A] × [B]**

$$-\frac{d[A]}{dt} = -\frac{d[B]}{dt} = k[A] \times [B]$$

bimolecular rate constant
1 / (concentration × time)

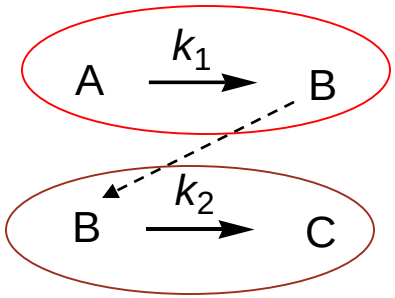
Theoretical foundations: *Mass Conservation Law*

Products are formed with the same rate as reactants disappear



$$-\frac{d[A]}{dt} = +\frac{d[P]}{dt} = +\frac{d[Q]}{dt}$$

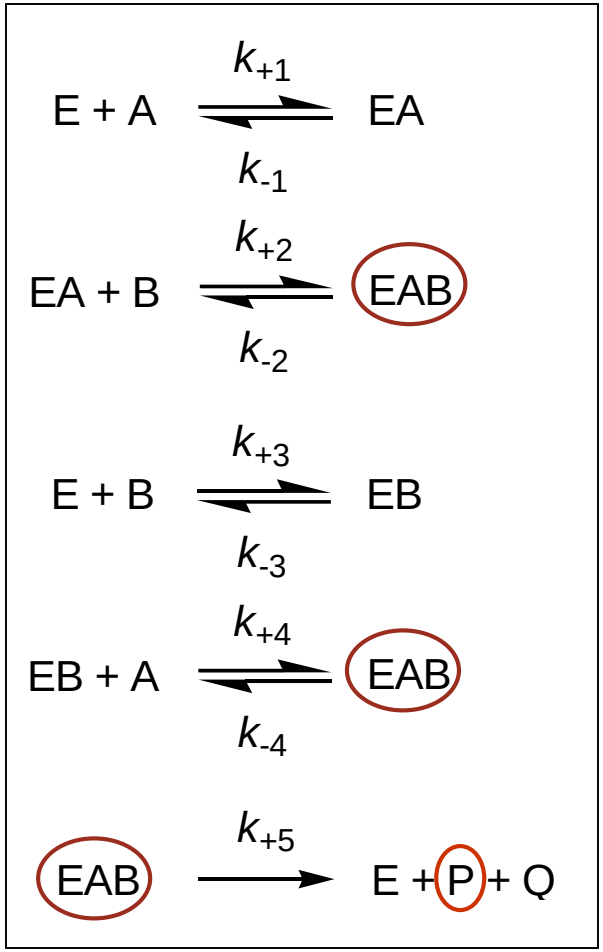
COMPOSITION RULE Additive terms from separate reactions



$$\frac{d[B]}{dt} = +k_1[A] - k_2[B]$$

Composition Rule: Example

EXAMPLE MECHANISM



RATE EQUATIONS

$$d[\mathbf{P}] / d\,t = + k_{+5}\,[\mathbf{EAB}]$$

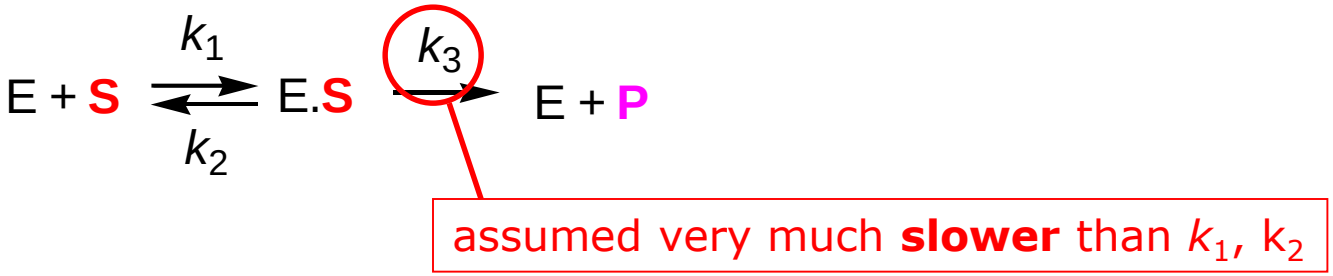
$$\begin{aligned} d[\mathbf{EAB}] / d\,t = \; & + k_{+2}\,[EA]\times[B] \\ & - k_{-2}\,[\mathbf{EAB}] \\ & + k_{+4}\,[EB]\times[A] \\ & - k_{-4}\,[\mathbf{EAB}] \\ & - k_{+5}\,[\mathbf{EAB}] \end{aligned}$$

Similarly for other species...

Initial rate kinetics

TWO BASIC APPROXIMATIONS

1. **Rapid-Equilibrium** Approximation

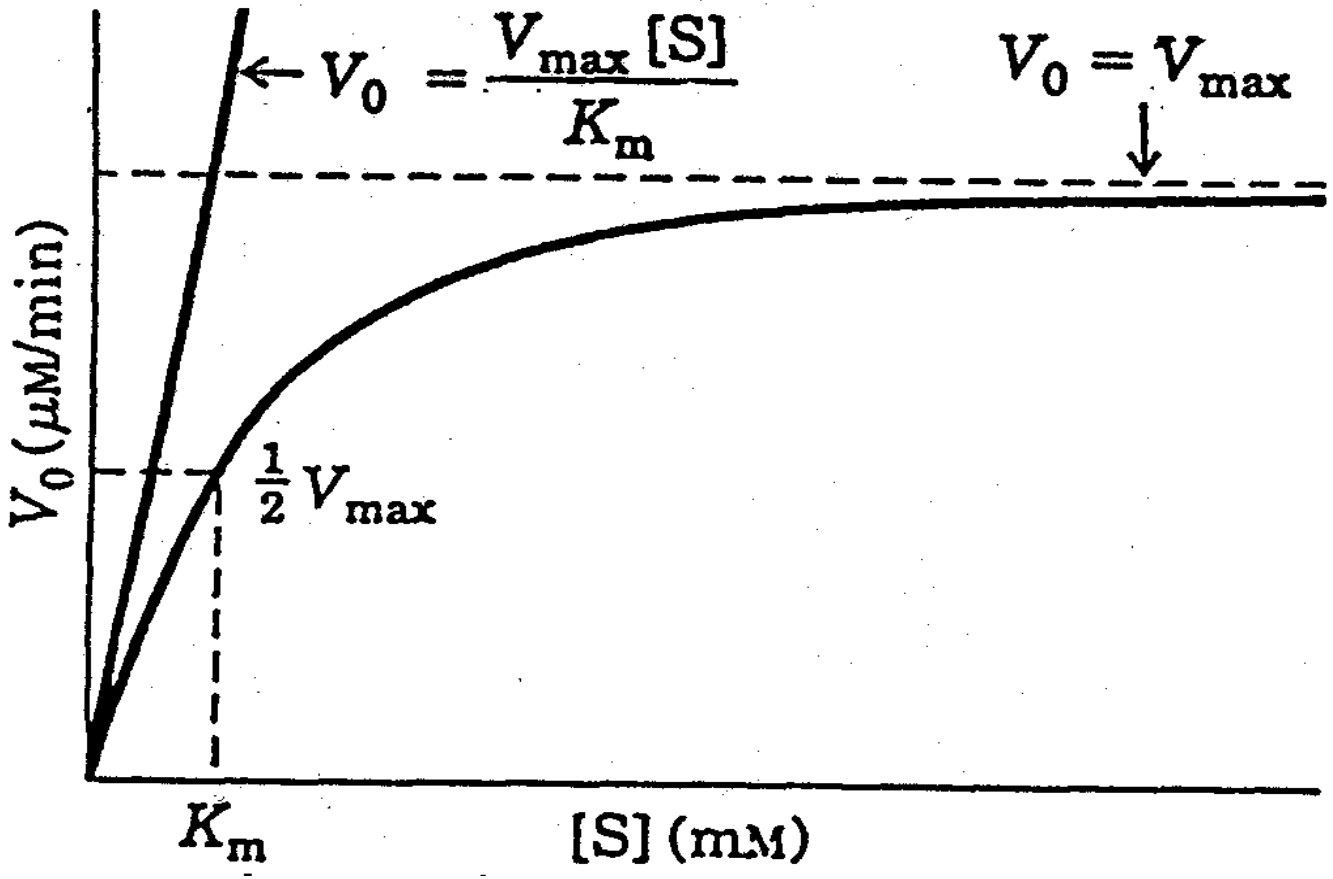


2. **Steady-State** Approximation

- *no assumptions* made about relative magnitude of k_1, k_2, k_3
- concentrations of enzyme forms are *unchanging*

Enzyme Kinetics
First example: Michaelis-Menton Kinetics

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



Michaelis-Menton Kinetics (Derivation)

E = enzyme concentration.

S = Substrate concentration.

ES = Enzyme-substrate complex concentration (noncovalent)

P = product concentration.

k_1 = rate constant for formation of ES from E + S.

k_{-1} = rate constant for decomposition of ES to E + S.

k_2 = rate constant for decomposition of ES to E + P.

Michaelis-Menton Kinetics (Derivation)

1. The overall rate of product formation: $v = k_2 [ES]$

2. Rate of formation of [ES]: $v_f = k_1[E][S]$

3. Rate of decomposition of [ES]:

$$v_d = k_{-1}[ES] + k_2 [ES]$$

4. The steady state assumption requires that:
   Rate of ES formation = Rate of ES decomposition

5. So: $k_1[E][S] = k_{-1}[ES] + k_2 [ES]$

Michaelis-Menton Kinetics (Derivation)

6. In solving for [ES], use the enzyme balance to eliminate [E].

$$E_T = [E] + [ES]$$

7. $$k_1 (E_T - [ES])[S] = k_{-1}[ES] + k_2 [ES]$$

$$k_1 E_T[S] - k_1[ES][S] = k_{-1}[ES] + k_2 [ES]$$

8. Rearrange and combine [ES] terms:

$$k_1 E_T[S] = (k_{-1} + k_2 + k_1 [S])[ES]$$

9. Solve for $[ES] = \dfrac{k_1 E_T[S]}{(k_{-1} + k_2 + k_1 [S])}$

Michaelis-Menton Kinetics (Derivation)

10. Divide through by k_1: $[ES] = \dfrac{E_T[S]}{(k_{-1} + k_2)/k_1 + [S]}$

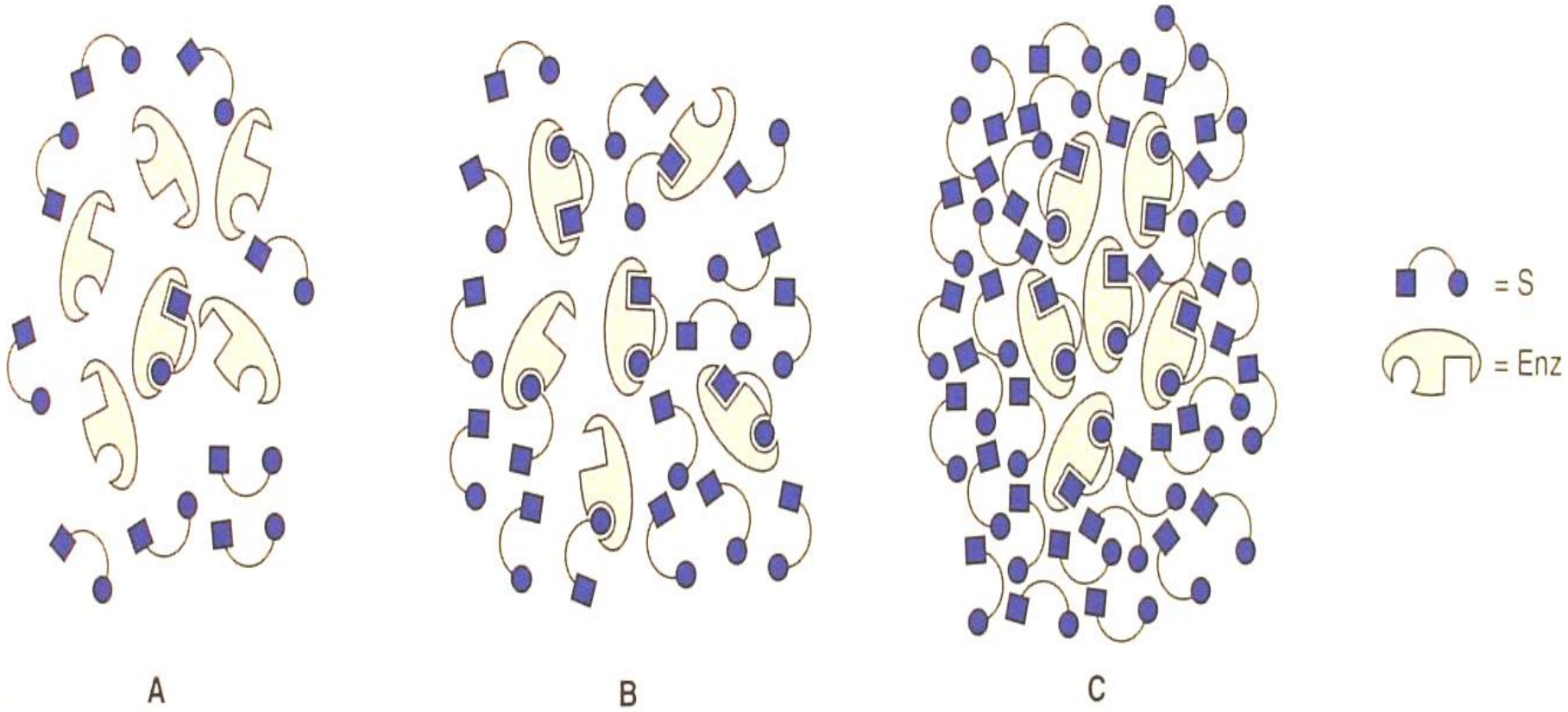
11. Definition of Michaelis constant: $K_M = (k_{-1} + k_2) / k_1$

12. Substitute K_M into the equation in step 10.

13. Then substitute [ES] into $v = k_2 [ES]$ from step1 and replace V_{max} with $k_2 E_T$ to give:

$$\mathbf{v = \frac{V_{max}[S]}{K_M + [S]}}$$

Meaning of K_m: Substrate Saturation of an Enzyme



Low [S] 50% [S] or K_m High, saturating [S]

Meaning of K_m

- An important relationship that can be derived from the Michaelis-Menten equation is the following:
- If **v_o is set equal to 1/2 V_{max}**, then the relation

  $V_{max}/2 = V_{max}[S]/K_m + [S]$ can be simplified to $K_m + [S] = 2[S]$, or $K_m = [S]$.
- This means that at one half of the maximal velocity, the substrate concentration at this velocity will be equal to the K_m. This relationship has been shown experimentally to be valid for many enzymes much more complex in regards to the number of substrates and catalytic steps than the simple single substrate model used to derive it.

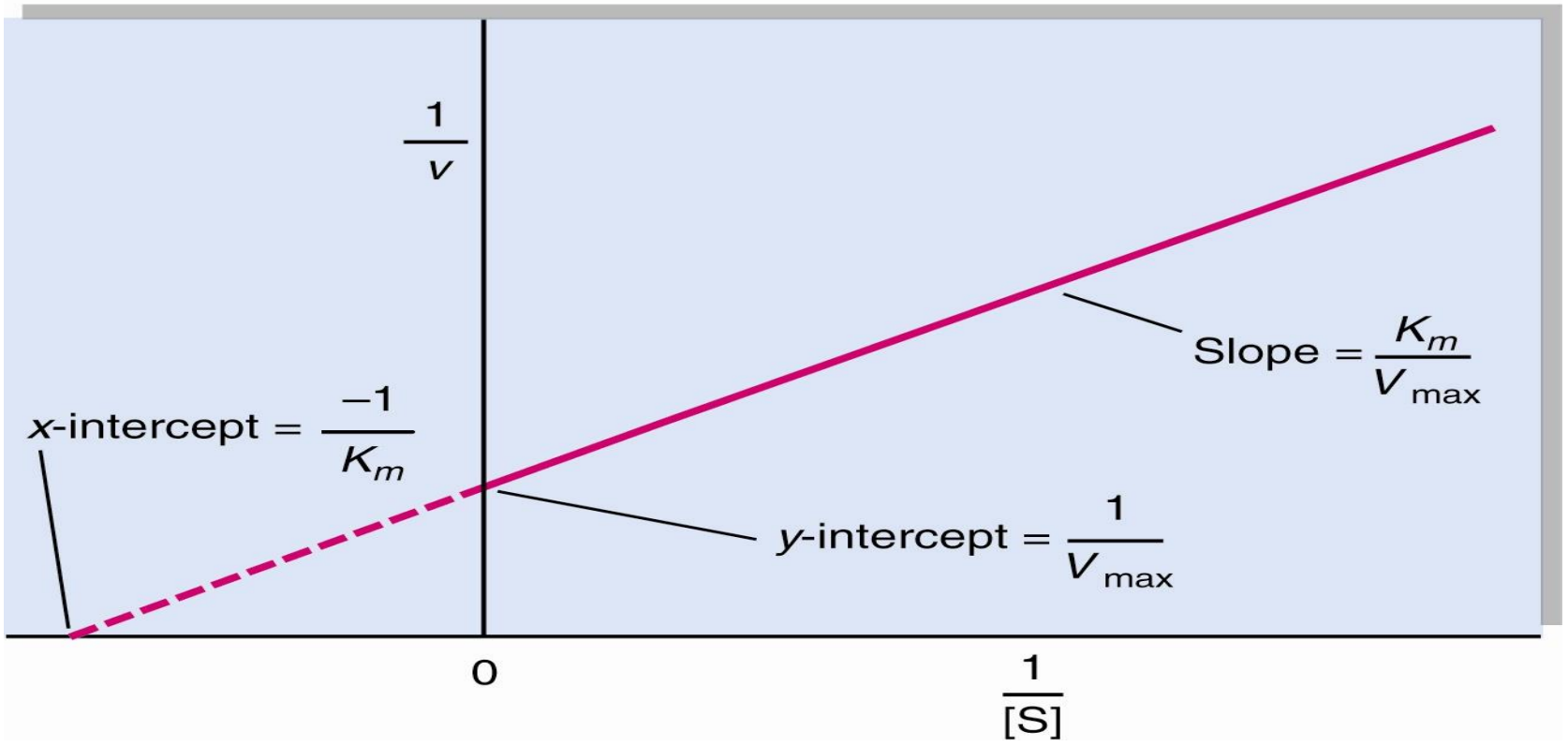
Uses of K_m

- Experimentally, K_m is a useful parameter for characterizing the number and/or types of substrates that a particular enzyme will utilize.
- It is also useful for comparing similar enzymes from different tissues or different organisms.
- Also, it is the K_m of the rate-limiting enzyme in many of the biochemical metabolic pathways that determines the amount of product and overall regulation of a given pathway.
- Clinically, K_m comparisons are useful for evaluating the effects mutations have on protein function for some inherited genetic diseases.

Michaelis-Menten Equation - Linear Plot

- Lineweaver-Burk:
- Begin with $v = V_{max}[S]/(K_m + [S])$ and take the reciprocal of both sides.

$$\frac{1}{v} = \frac{K_m}{V_{max}}\left(\frac{1}{[S]}\right) + \frac{1}{V_{max}}$$

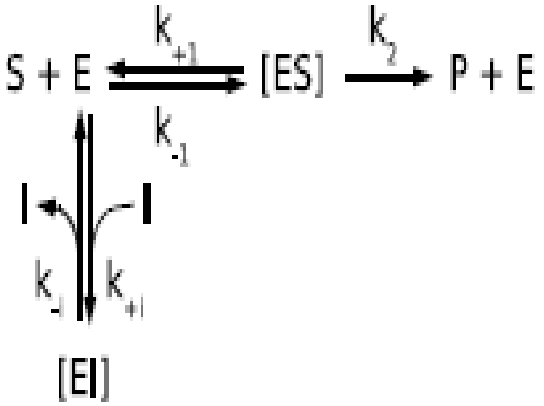


Enzyme Inhibitor Types

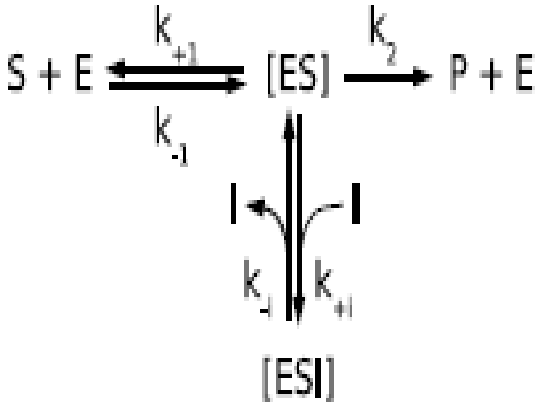
- Inhibitors of enzymes are generally molecules which resemble or mimic a particular enzymes substrate(s). Therefore, it is not surprising that many therapeutic drugs are some type of enzyme inhibitor.

- The modes and types of inhibitors have been classified by their kinetic activities and sites of actions. These include Reversible Competitive Inhibitors, Reversible Uncompetitive Inhibitors, and Reversible Non-Competitive Inhibitors.

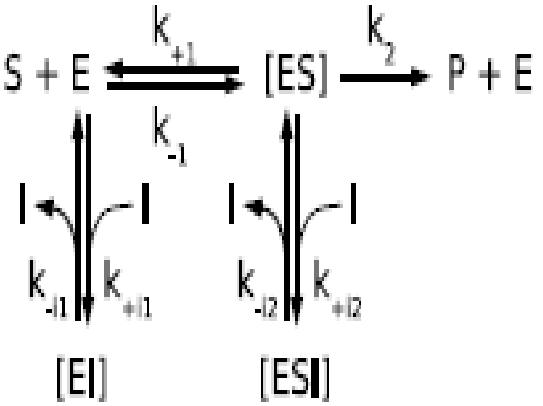
A: competitive inhibition



B: uncompetitive inhibition

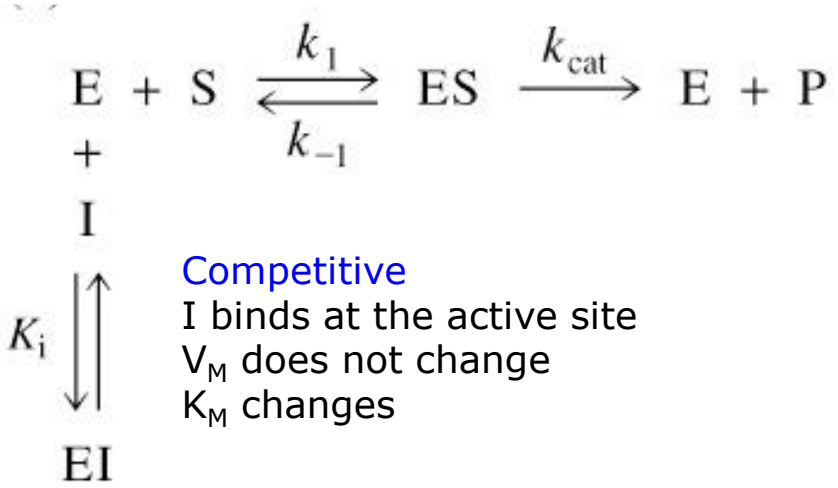


C: noncompetitive inhibition

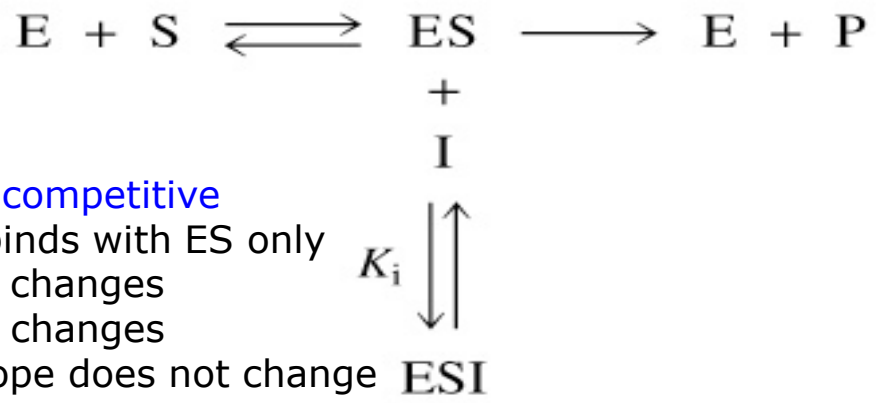


Type	Irreversible	Reversible
competitive	$\nu = \frac{V_M [S]}{K_M \left(1 + \frac{[I]}{K_I}\right) + [S]}$	$\nu = \frac{V_{m_+} \frac{[S]}{K_S} - V_{m_-} \frac{[P]}{K_P}}{1 + \frac{[S]}{K_M} + \frac{[P]}{K_P} + \frac{[I]}{K_I}}$
uncompetitive	$\nu = \frac{V_M [S]}{K_M + [S] \left(1 + \frac{[I]}{K_I}\right)}$	$\nu = \frac{V_{m_+} \frac{[S]}{K_S} - V_{m_-} \frac{[P]}{K_P}}{1 + \left(\frac{[S]}{K_M} + \frac{[P]}{K_P}\right) \left(1 + \frac{[I]}{K_I}\right)}$
noncompetitive	$\nu = \frac{V_M [S]}{\left(1 + \frac{[I]}{K_I}\right) (K_M + [S])}$	$\nu = \frac{V_{m_+} \frac{[S]}{K_S} - V_{m_-} \frac{[P]}{K_P}}{\left(1 + \frac{[S]}{K_M} + \frac{[P]}{K_P}\right) \left(1 + \frac{[I]}{K_I}\right)}$

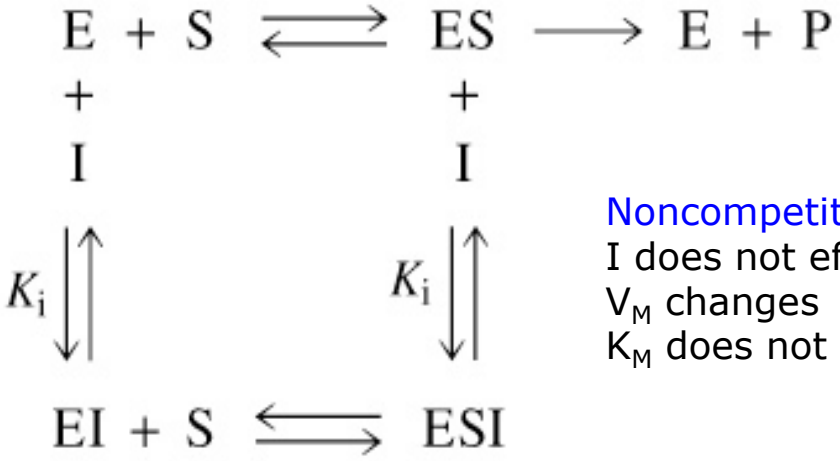
Enzyme Inhibitor Types



Competitive
I binds at the active site
V_M does not change
K_M changes



Uncompetitive
I binds with ES only
V_M changes
K_M changes
Slope does not change



Noncompetitive
I does not effect binding of S
V_M changes
K_M does not change

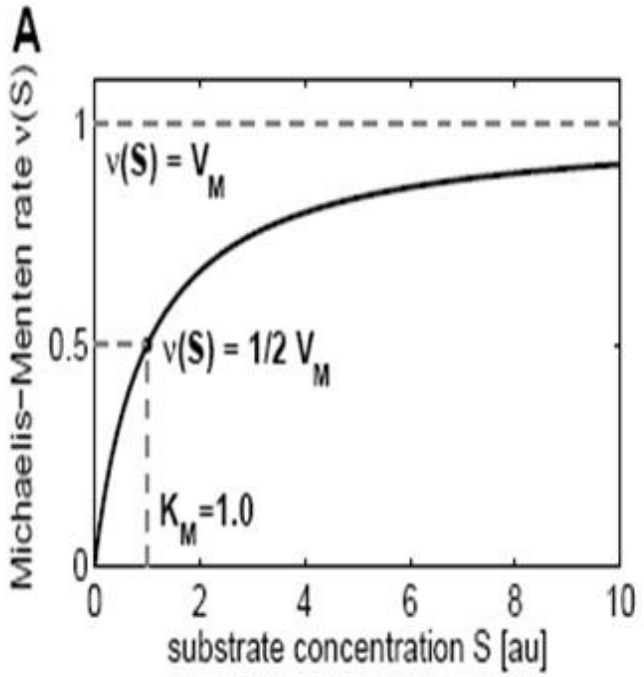
K_i

- **K_i values** are used to characterize and compare the effectiveness of inhibitors relative to K_m.
- This parameter is especially useful and important in evaluating the potential therapeutic value of inhibitors (drugs) of a given enzyme reaction.
- For example, K_i values are used for comparison of the different types of HIV protease inhibitors.
- In general, the lower the K_i value, the tighter the binding, and hence the more effective an inhibitor is.

Rate Equations (Summary)

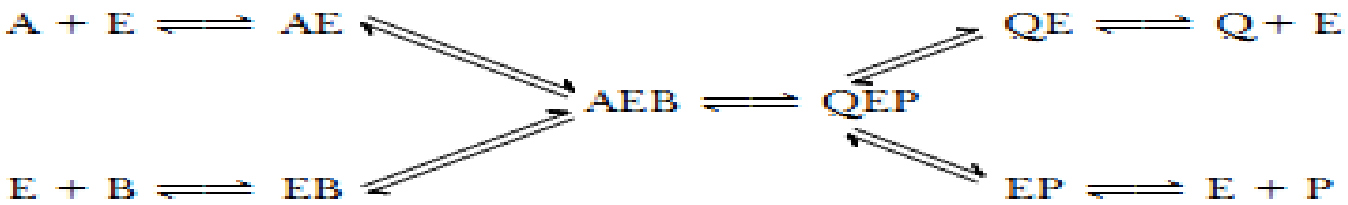
Michaelis-Menten

$$v = \frac{d[P]}{dt} = \frac{k_2[E]_t[S]}{s + \frac{k_{-1}+k_2}{k_1}} = \frac{V_{max}[S]}{S + K_m}$$

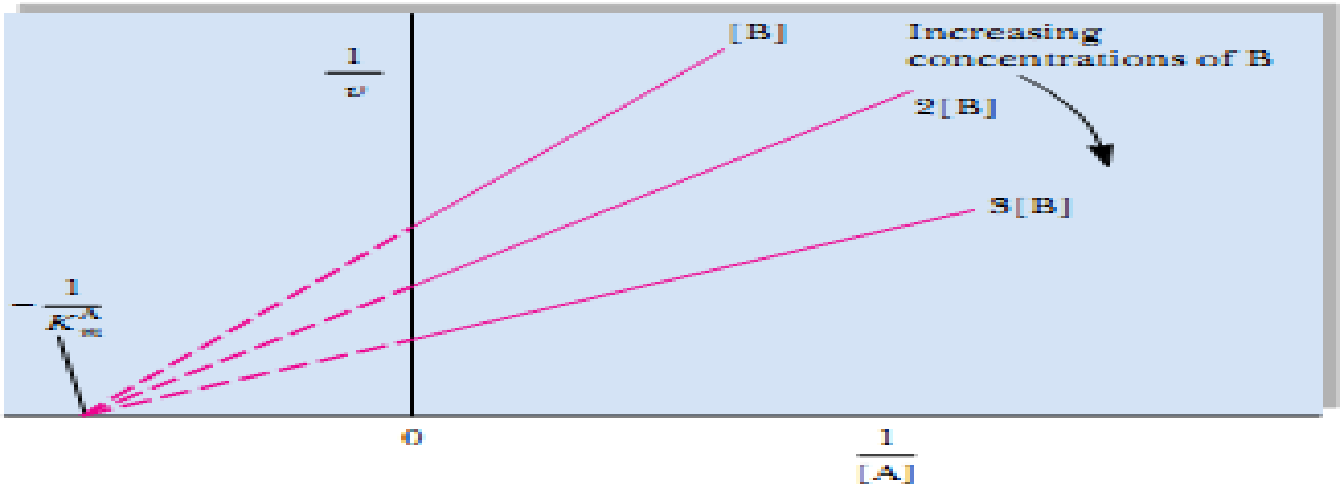


Rate Equations (Summary)

Random Mechanism

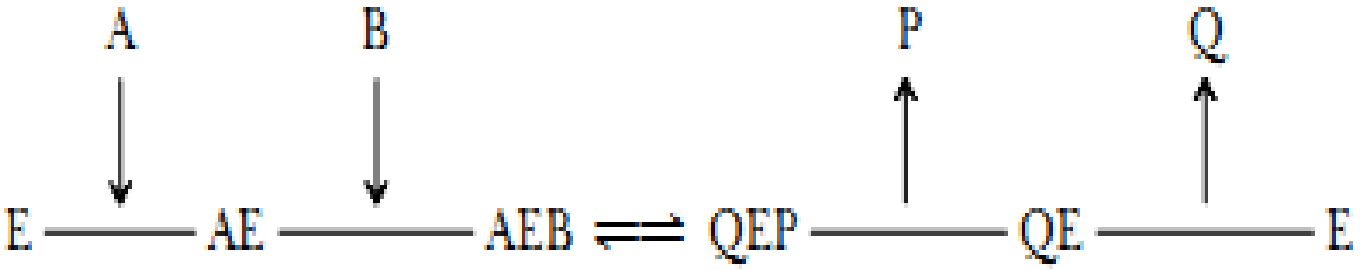


$$\frac{1}{v} = \frac{K_{mA}}{V_1[A]} + \frac{K_{mB}}{V_1[B]} + \frac{1}{V_1}$$



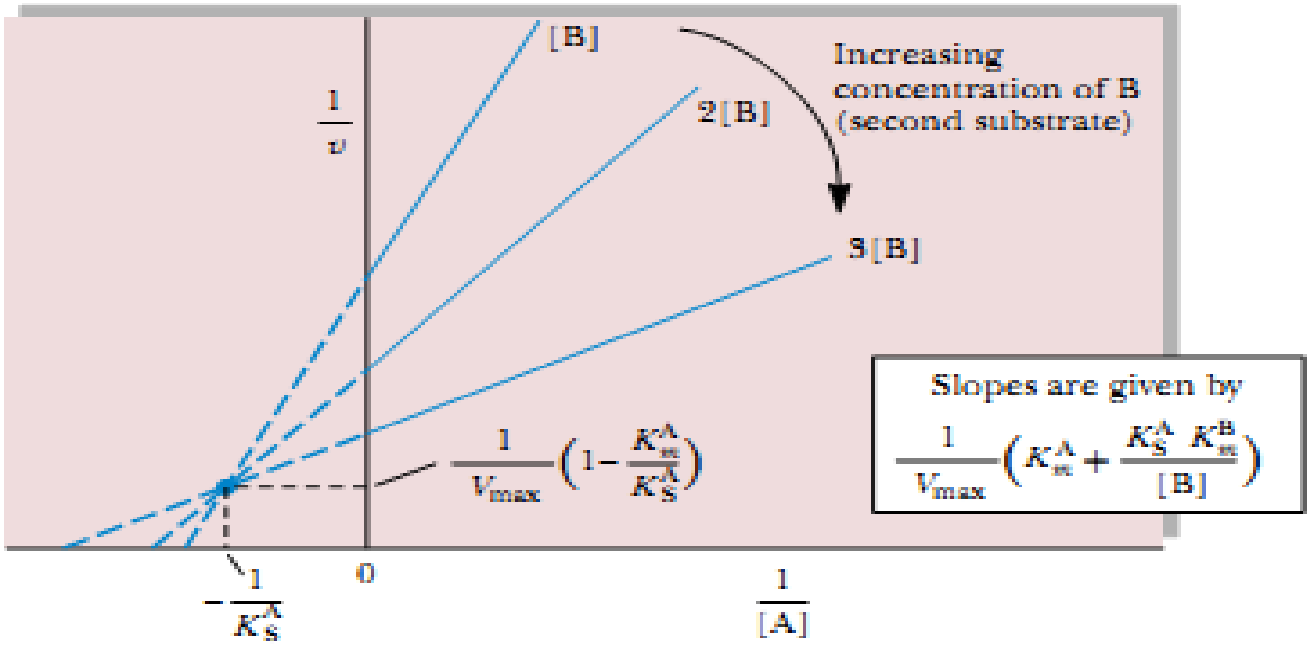
Rate Equations (Summary)

Ordered Mechanism



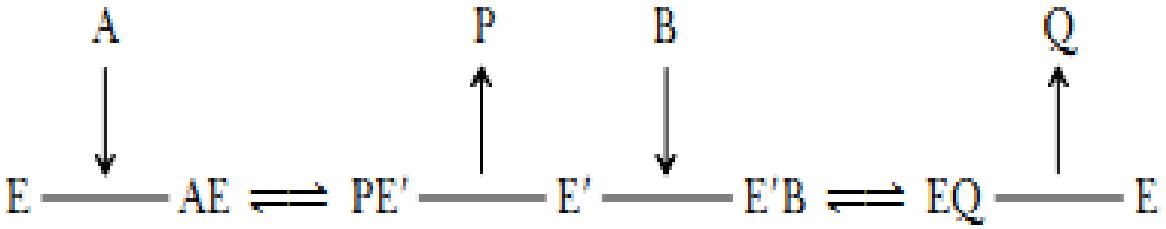
Double-reciprocal form of the rate equation:

$$\frac{1}{v} = \frac{1}{V_{max}}\left(K_m^A + \frac{K_S^A\, K_m^B}{[B]}\right)\left(\frac{1}{[A]} + \frac{1}{V_{max}}\left(1 + \frac{K_m^B}{[B]}\right)\right)$$

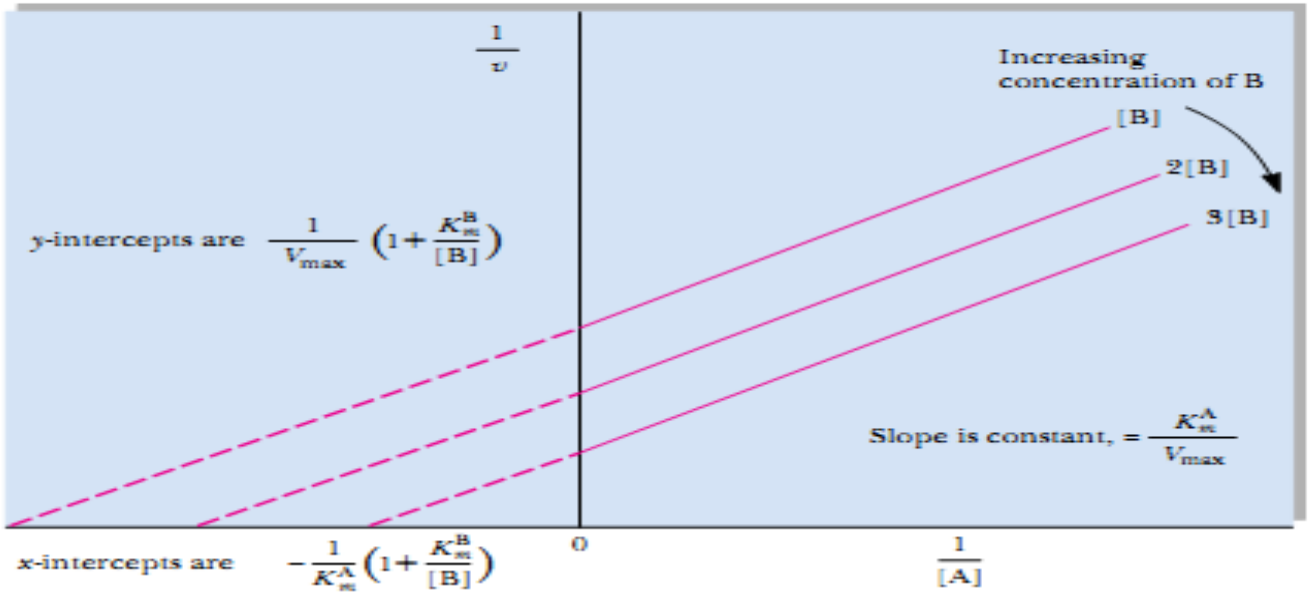


Rate Equations (Summary)

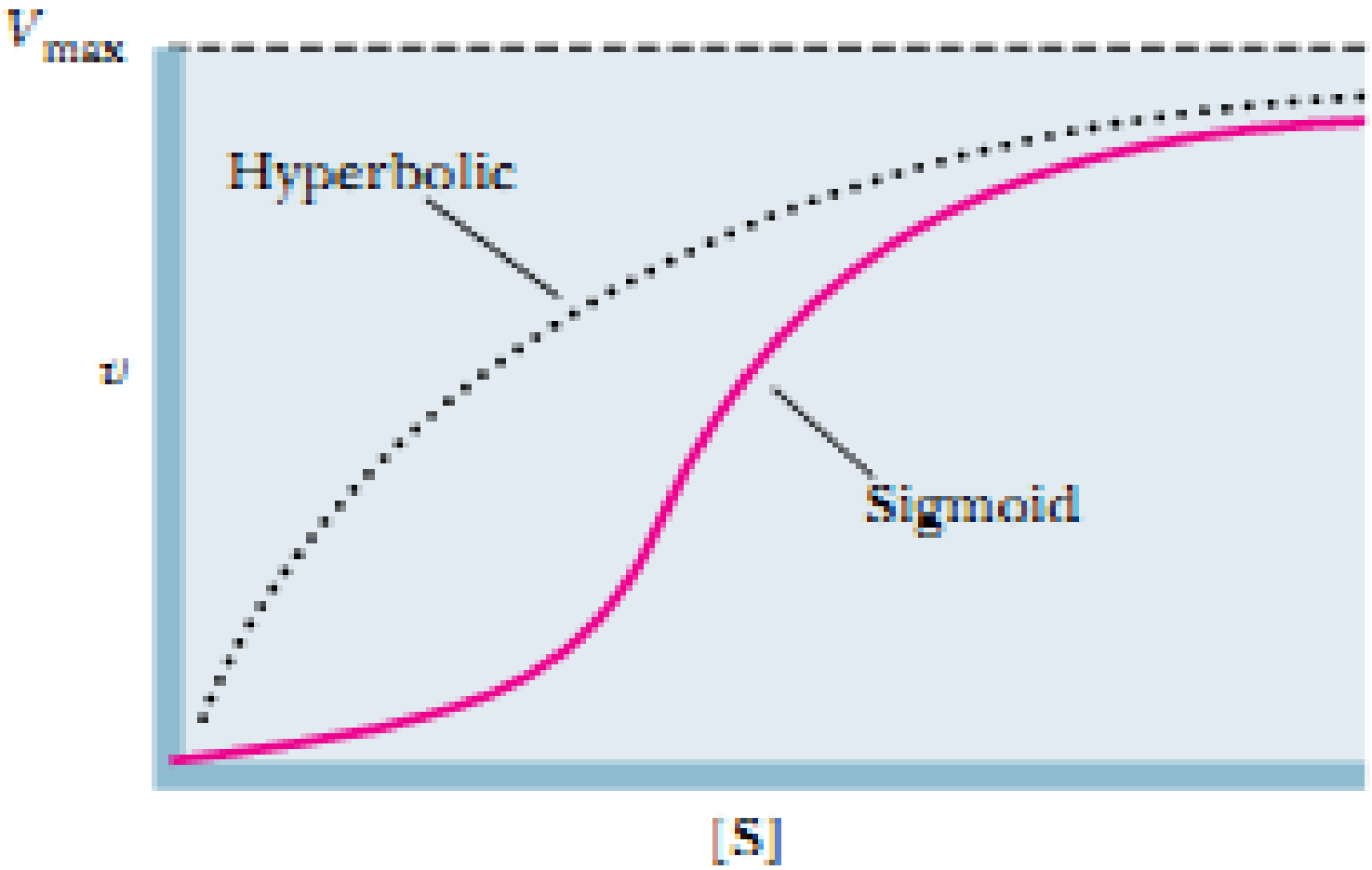
Ping-Pong Mechanism



Double-reciprocal form of the rate equation: $\frac{1}{v} = \frac{K_m^A}{V_{max}}\left(\frac{1}{[A]}\right) + \left(1 + \frac{K_m^B}{[B]}\right)\left(\frac{1}{V_{max}}\right)$

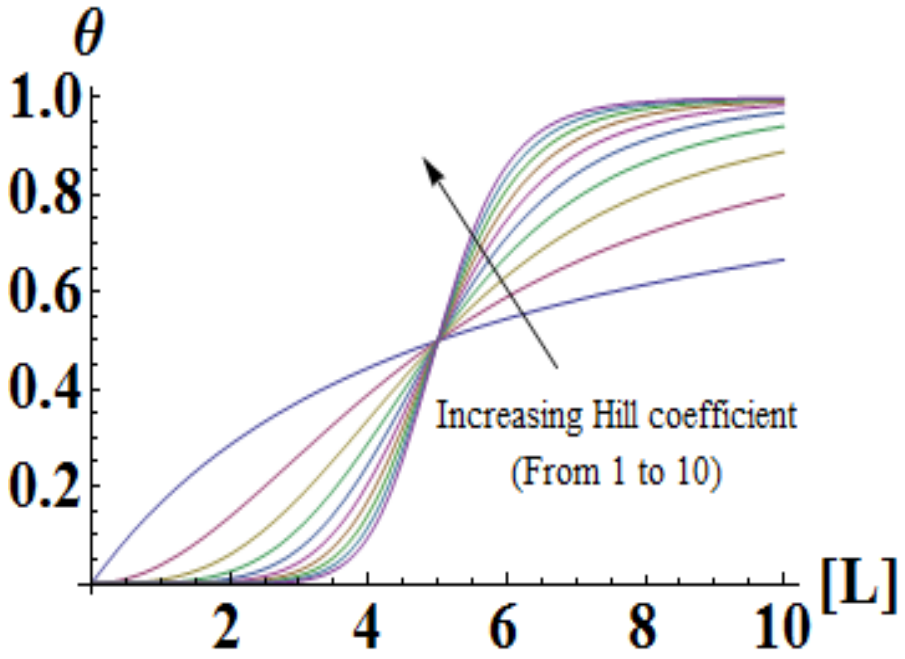


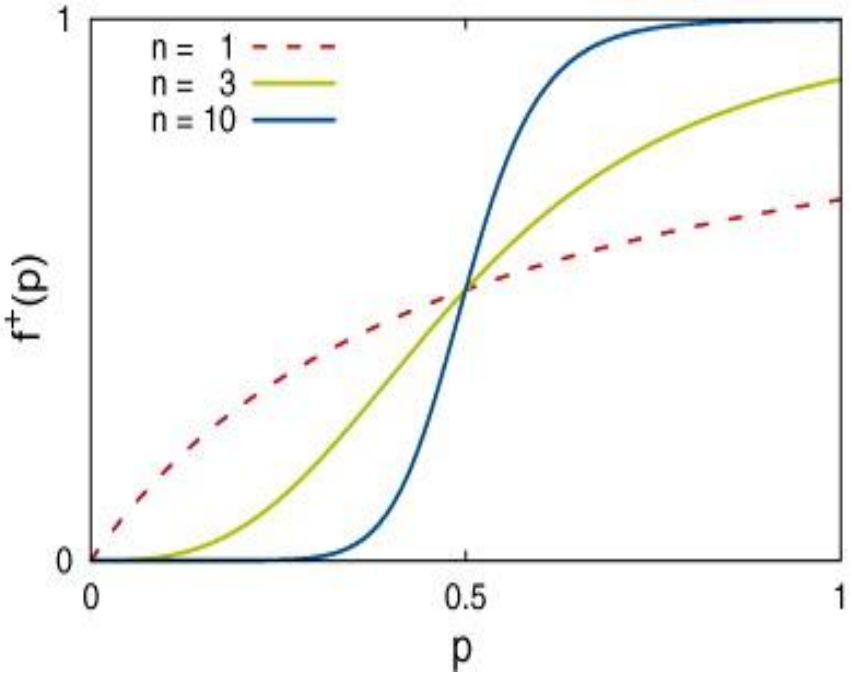
Allosteric enzymes



Rate Equations (Summary)

Hill Equation





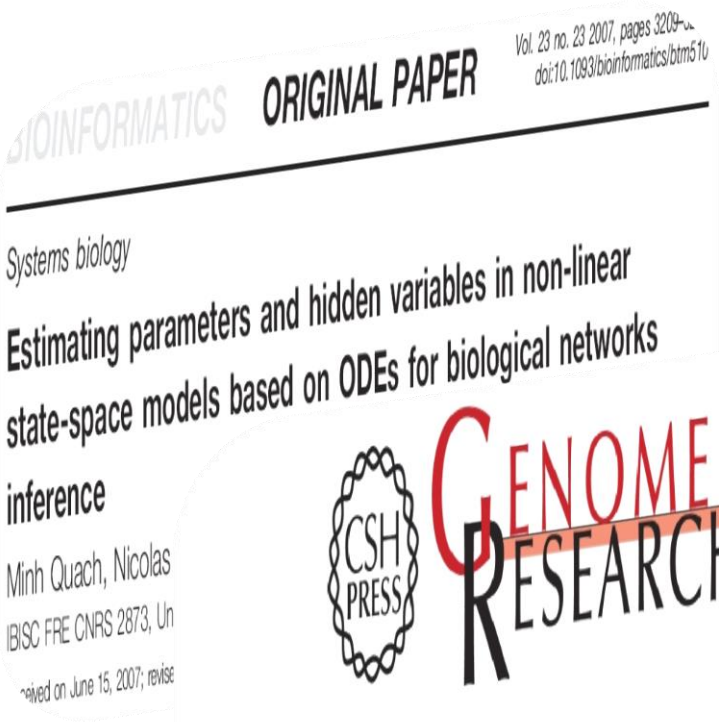
$$V = \frac{V_{\max}[S]^n}{(K_{0.5})^n + [S]^n}$$

Rate Equations (Summary)

General Equation

$$\nu_{generic}(\mathbf{S},\mathbf{P}) = \frac{V \prod_{m_+} \prod_i [S]_i - V \prod_{m_-} \prod_j [P]_j}{F(\mathbf{S},\mathbf{P},\mathbf{K})}$$

Parameter Estimation


BIOINFORMATICS ORIGINAL PAPER

Vol. 23 no. 23 2007, pages 3209–3
doi:10.1093/bioinformatics/btm51

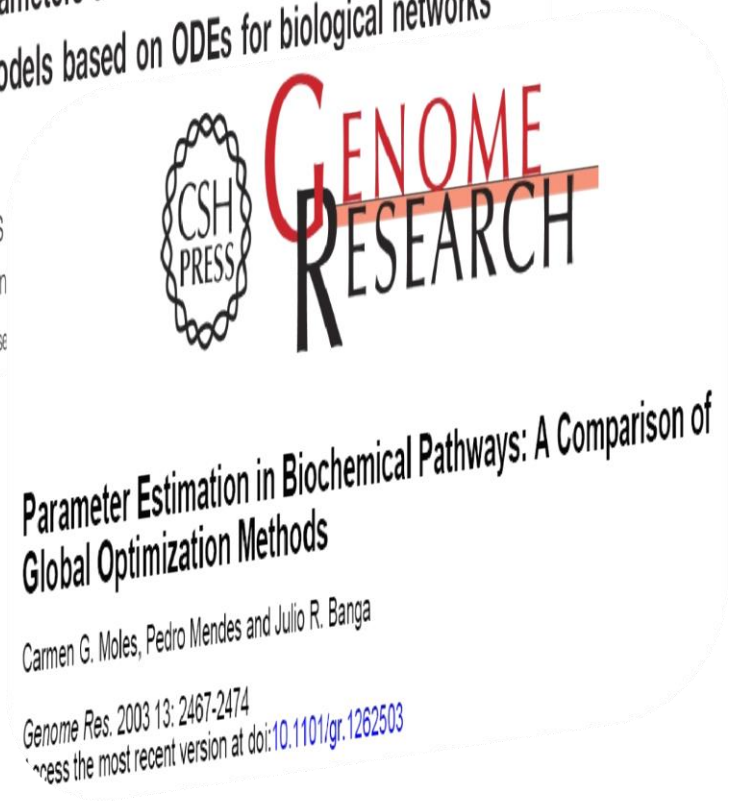
Systems biology

Estimating parameters and hidden variables in non-linear state-space models based on ODEs for biological networks inference

Minh Quach, Nicolas

IBISC FRE CNRS 2873, Un

eived on June 15, 2007; revise


CSH PRESS

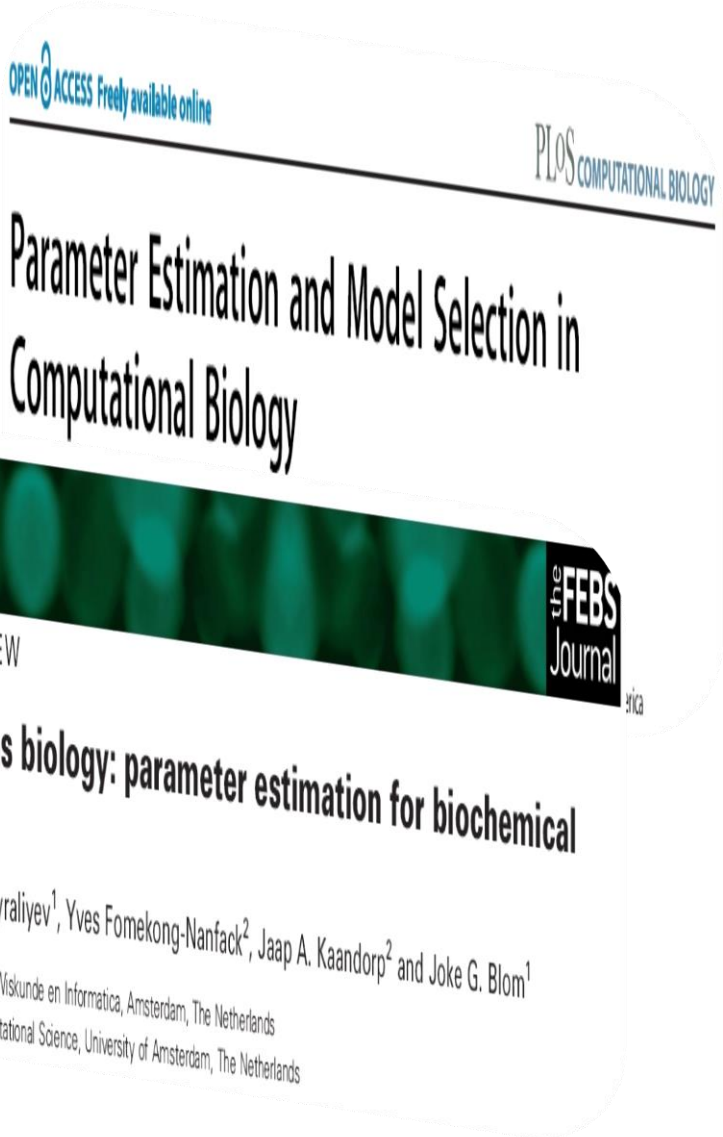
GENOME RESEARCH

Parameter Estimation in Biochemical Pathways: A Comparison of Global Optimization Methods

Carmen G. Moles, Pedro Mendes and Julio R. Banga

Genome Res. 2003 13: 2467-2474

ccess the most recent version at doi:10.1101/gr.1262503


OPEN ACCESS Freely available online

PLoS COMPUTATIONAL BIOLOGY

Parameter Estimation and Model Selection in Computational Biology

MINIREVIEW

the FEBS Journal

Systems biology: parameter estimation for biochemical models

Maksat Ashyraliyev[1], Yves Fomekong-Nanfack[2], Jaap A. Kaandorp[2] and Joke G. Blom[1]

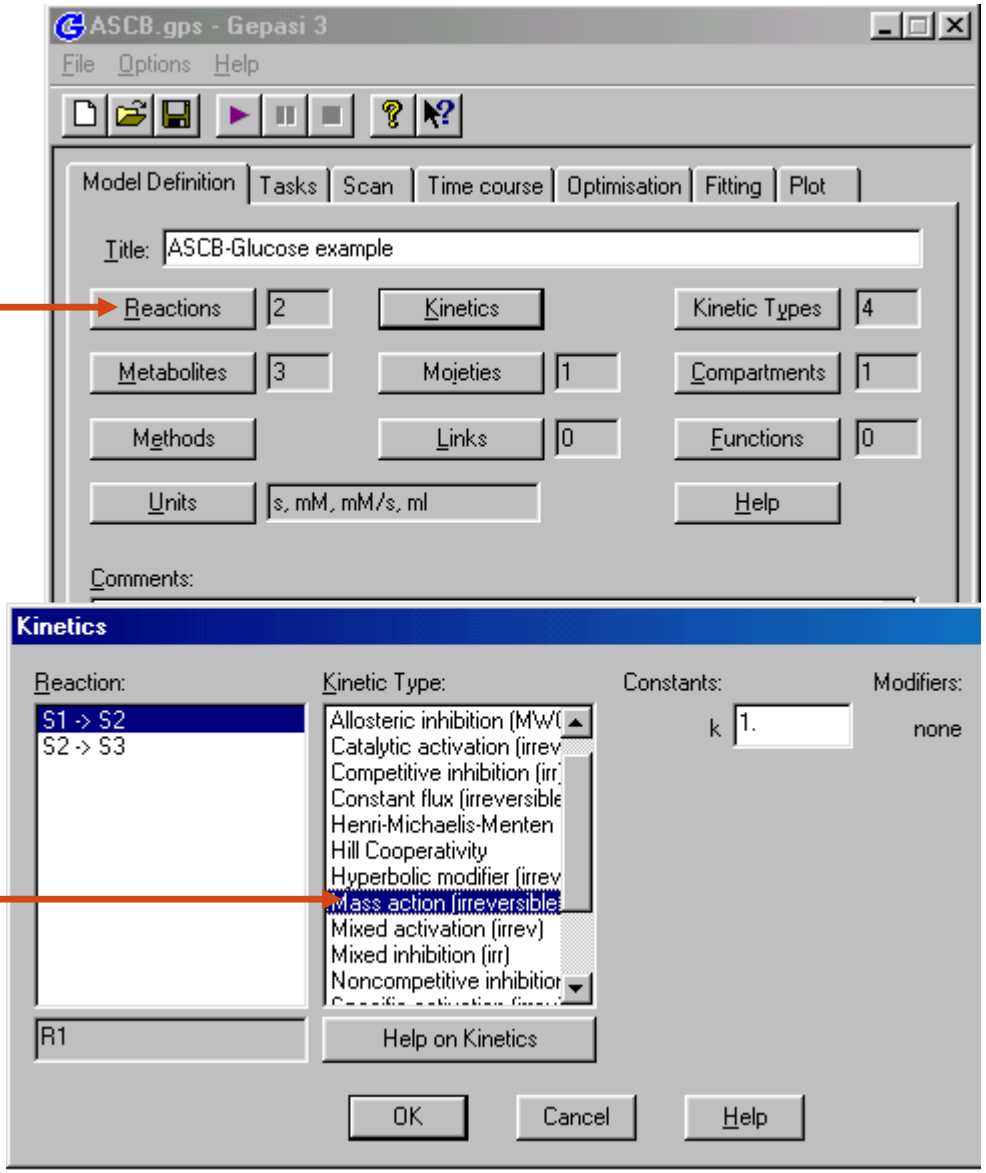
1 Centrum voor Wiskunde en Informatica, Amsterdam, The Netherlands

ction Computational Science, University of Amsterdam, The Netherlands

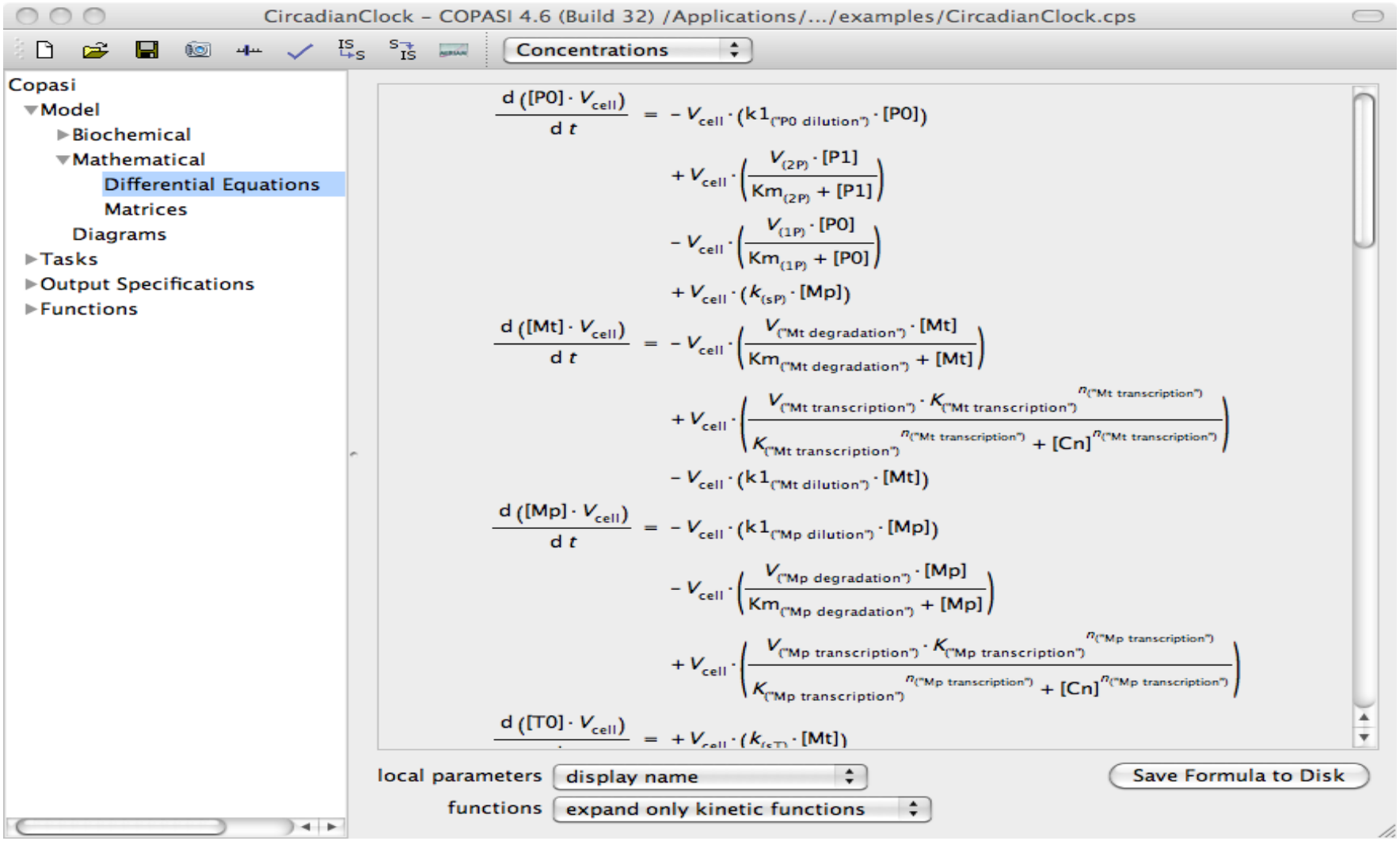
Software: Gepasi

Chemical Equations

Math



Software: Copasi



Practical Session: Examples

- Brusselator
- Peroxidase activity & oscillatory dynamics *(Eur. J. Biochem.-2003)*
- Glycolysis *(Eur. J. Biochem.-2003)*
- Ultrasensitivity in the MAPK cascade *(PNAS-1996)*
- Oscillations in NF-κB Signaling *(Science-2004)*