Master – First Year

LOGISTIC ENZYME KINETICS: THE FIRST SPECIFIC INTERACTION

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MICHAELIS-MENTEN EQUATION

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

$$\frac{d}{dt}[S] = -k_1[E][S] + k_{-1}[ES]$$

$$\frac{d}{dt}[E] = -k_1[E][S] + (k_{-1} + k_2)[ES]$$

$$\frac{d}{dt}[ES] = k_1[E][S] - (k_{-1} + k_2)[ES]$$

$$\frac{d}{dt}[P] = k_2[ES]$$

$$[E](t) + [ES](t) = [E_0]$$

$$[S](t) + [ES](t) + [P](t) = [S_0]$$

$$\frac{d}{dt}[S] = -k_1[S]([E_0] - [ES]) + k_{-1}[ES]$$

$$\frac{d}{dt}[ES] = k_1[S]([E_0] - [ES]) - (k_{-1} + k_2)[ES]$$

quasi-steady-state (or equilibrium) *approximation* (QSSA)

$$\frac{d}{dt}[ES] \cong 0$$

$$\frac{d}{dt}[S] = -\frac{V_{\max}[S]}{[S] + K_M}$$

$$v = \frac{d}{dt}[P] = \frac{V_{\max}[S]}{[S] + K_M}$$

$$V_{\max} = k_2[E_0]$$

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

$$[ES] = \frac{[E_0][S]}{[S] + K_M}$$

$$[ES](t) = \frac{[E_0][S]}{[S] + K_M}\{1 - \exp[-k_1 t([S_0] + K_M)]\} \; , 0 \le t < \infty$$

SCHNELL AND MENDOZA W-LAMBERT SOLUTION

$$\frac{d}{dt}[S] = -\frac{V_{\max}[S]}{[S]+K_M}$$

$$\left(\frac{K_M}{[S]}+1\right)d[S] = -V_{\max}dt$$

integrated to give

$$[S]+K_M\ln[S] = [S_0]-V_{\max}t+K_M\ln[S_0]$$

double plot equation

$$\frac{t}{[S_0]-[S](t)} = \frac{1}{V_{\max}}+\frac{K_M}{V_{\max}}\left(\frac{1}{[S_0]-[S](t)}\ln\frac{[S_0]}{[S](t)}\right)$$

With the substitution

$$\varphi([S]) = \frac{[S]}{K_M}$$

$$\varphi([S])+\ln\varphi([S]) = \frac{[S_0]}{K_M}-\frac{V_{\max}t}{K_M}+\ln\left(\frac{[S_0]}{K_M}\right)$$

analogy with the famous Lambert type equation

$$W(x)+\ln W(x) = \ln x\,,\quad x\geq -1/e$$

$$[S]_W(t) = K_M W\left(\frac{[S_0]}{K_M}e^{\frac{[S_0]-V_{\max}t}{K_M}}\right)$$

LOGISTIC ENZYME KINETICS

$$1 = P_{REACT}([S]_{bind}) + P_{UNREACT}([S]_{bind})$$

$$P_{REACT}([S]_{bind}) = \begin{cases} 0 \ , & [S]_{bind} \to 0 \\ 1 \ , & [S]_{bind} >> 0 \end{cases}$$

$$P_{UNREACT}([S]_{bind}) = \begin{cases} 1 \ , & [S]_{bind} \to 0 \\ 0 \ , & [S]_{bind} >> 0 \end{cases}$$

$$[S]_{bind} = [S](t)$$

$$P_{REACT}([S](t)) = \frac{v(t)}{V_{\max}} = -\frac{1}{V_{\max}}\frac{d}{dt}[S](t)$$

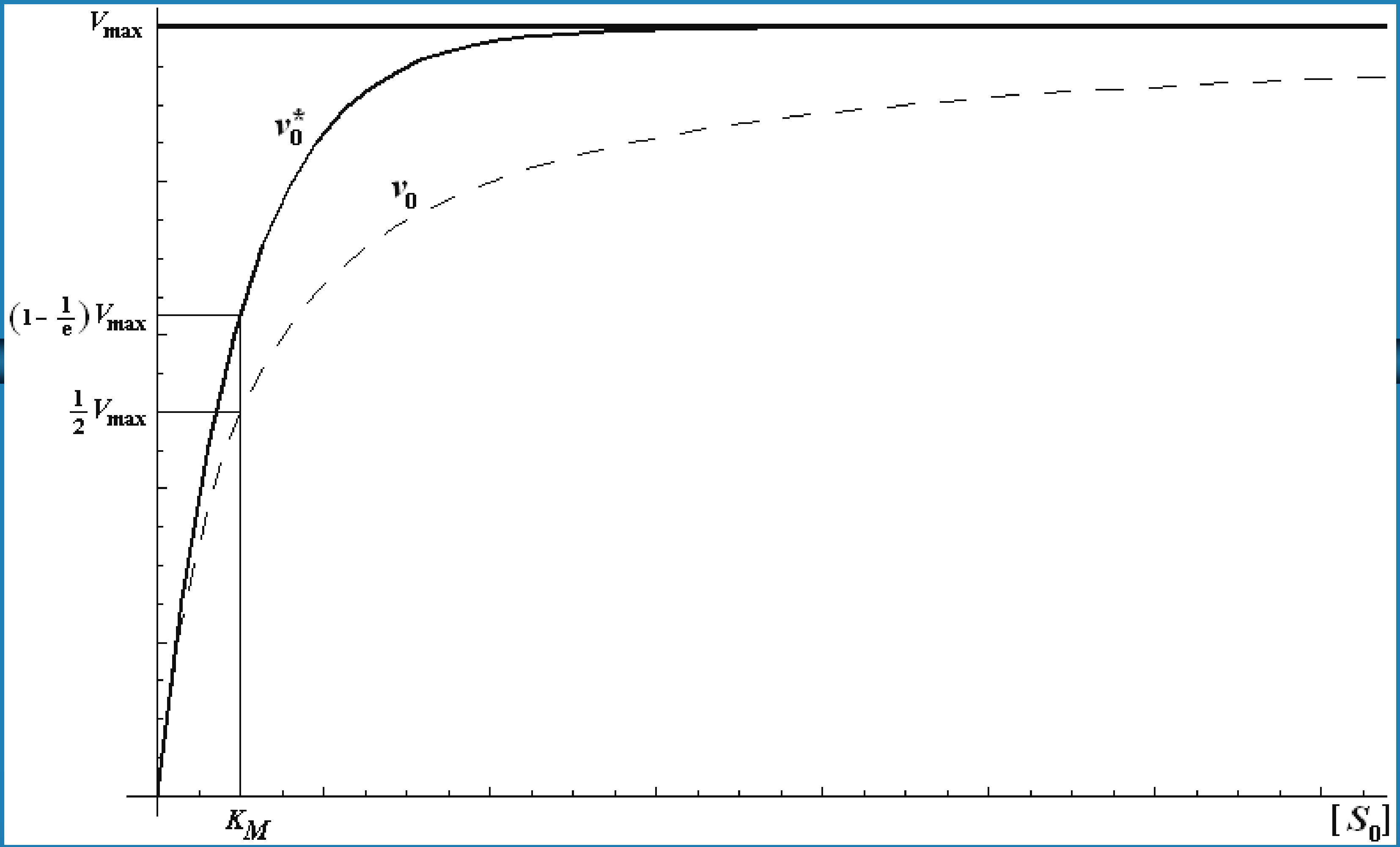
$$P_{UNREACT}([S](t))^{MM} = \frac{K_M}{[S](t) + K_M}$$

$$P_{UNREACT}([S](t))^{*} = e^{-\frac{[S](t)}{K_M}}$$

$$\frac{d}{dt}[S] = -\frac{V_{\max}[S]}{[S] + K_M}$$

$$-\frac{1}{V_{\max}}\frac{d}{dt}[S](t) = 1 - e^{-\frac{[S](t)}{K_M}}$$

$$P_{UNREACT}([S](t))^{*} = \frac{1}{e^{\frac{[S](t)}{K_M}}} \overset{[S](t)\to 0}{\cong} \frac{1}{1 + \frac{[S](t)}{K_M}} = P_{UNREACT}([S](t))^{MM}$$



$$v_0 = \frac{V_{max}[S_0]}{[S_0]+K_M}$$

$$v_0^* = V_{max}\left[1-\exp\left(-[S_0]/K_M\right)\right]$$

RELIABILITY OF THE LOGISTIC ENZYME KINETIC

Quasi Steady-State Approximation Analysis

QSSA is equivalent with the physiologically common condition
that the substrate is in great excess over the enzyme, as firstly shown by Laidler

$$[S_0] >> [E_0]$$

$$P_{\mathrm{REACT}}([S]_{bind}) \to 1 \Leftrightarrow P_{\mathrm{UNREACT}}([S]_{bind}) \to 0$$

$$P_{\mathrm{REACT}}([S](t)) = 1$$

$$-\frac{1}{V_{\max}} \frac{d}{dt}[S](t) = 1$$

$$V_{\max} = k_2[E_0] \qquad [S](t) = [S_0] - k_2[E_0]t \qquad [S](t) >> 0$$

$$t \cong \frac{1}{k_2}$$

$$P_{\mathrm{UNREACT}}([S](t))^{\mathrm{MM}} = \frac{1}{1 + \frac{[S](t)}{K_M}} > \frac{1}{e^{\frac{[S](t)}{K_M}}} = P_{\mathrm{UNREACT}}([S](t))^{*}$$

RELIABILITY OF THE LOGISTIC ENZYME KINETIC

Full Time Course Analysis

$$-\frac{1}{V_{\max}}\frac{d}{dt}[S](t)=1-e^{\frac{[S](t)}{K_M}}$$

$$\int_{[S_0]}^{[S](t)}\frac{d[S](t)}{\exp(-[S](t)/K_M)-1}=\int_0^t V_{\max}dt$$

$$[S_0]-[S](t)+K_M\ln\left(e^{\frac{[S_0]}{K_M}}-1\right)-K_M\ln\left(e^{\frac{[S](t)}{K_M}}-1\right)=V_{\max}t$$

$$\varphi([S](t))=\frac{[S](t)}{K_M}$$

$$\psi(t)=\frac{1}{K_M}(V_{\max}t-[S_0])-\ln\left(e^{\frac{[S_0]}{K_M}}-1\right)$$

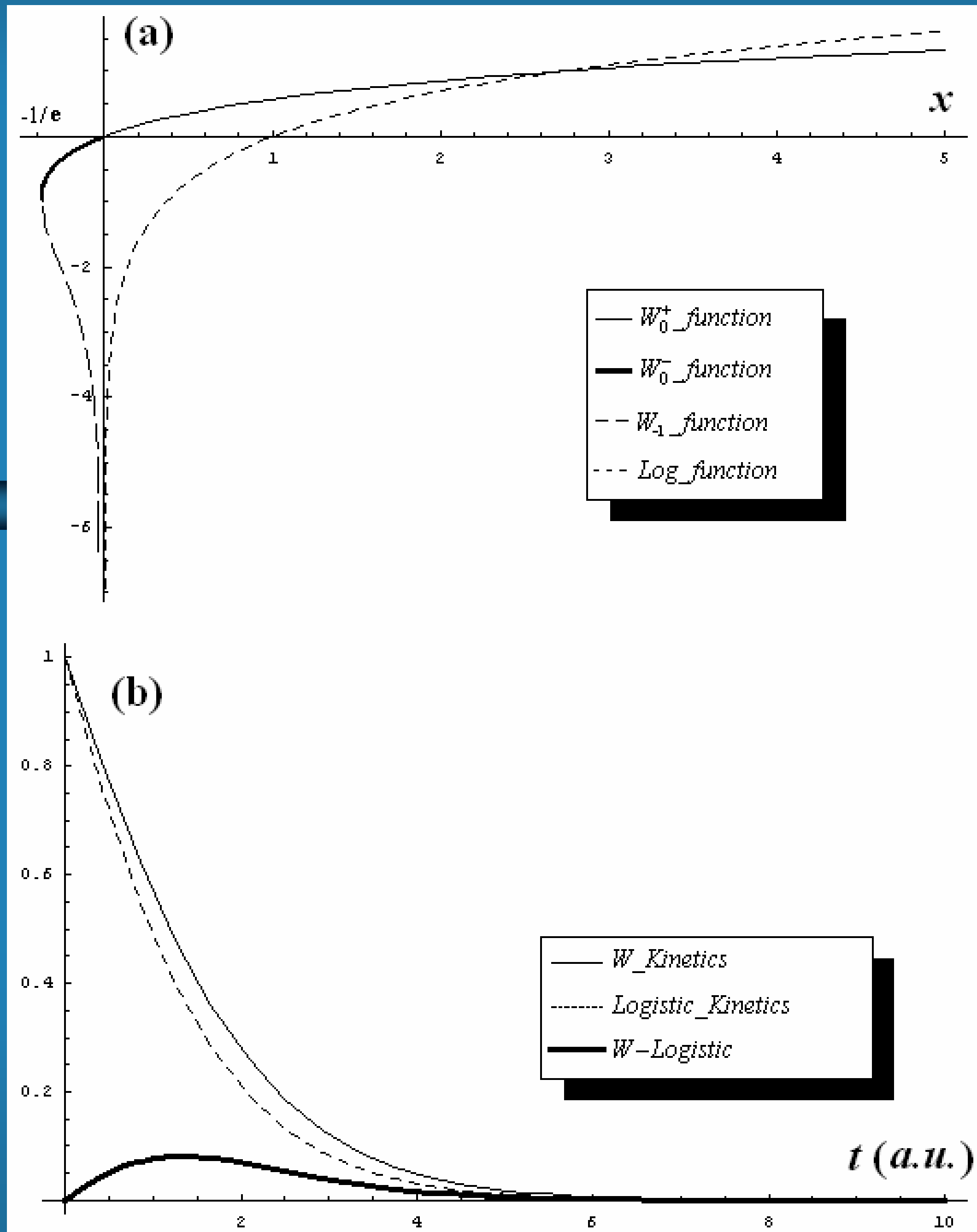
$$-\varphi([S](t))-\ln\left(e^{-\varphi([S](t))}-1\right)=\psi(t)$$

$$\varphi([S](t))=\ln\left(1-e^{-\psi(t)}\right)$$

$$[S]_L(t)=K_M\ln\left(1+e^{-\frac{V_{\max}t}{K_M}}\left(e^{\frac{[S_0]}{K_M}}-1\right)\right)$$

$$[S]_L(t)=\begin{cases}[S_0], t\to 0\\ 0 \quad , t\to\infty\end{cases}$$

GENERAL LOGISTIC TRANSFORMATION



$$f_1 W\left(f_2 e^{f_2} e^{-f_3 t}\right)$$

$$f_1 \ln\left(1+\left(e^{f_2}-1\right)e^{-f_3 t}\right)$$

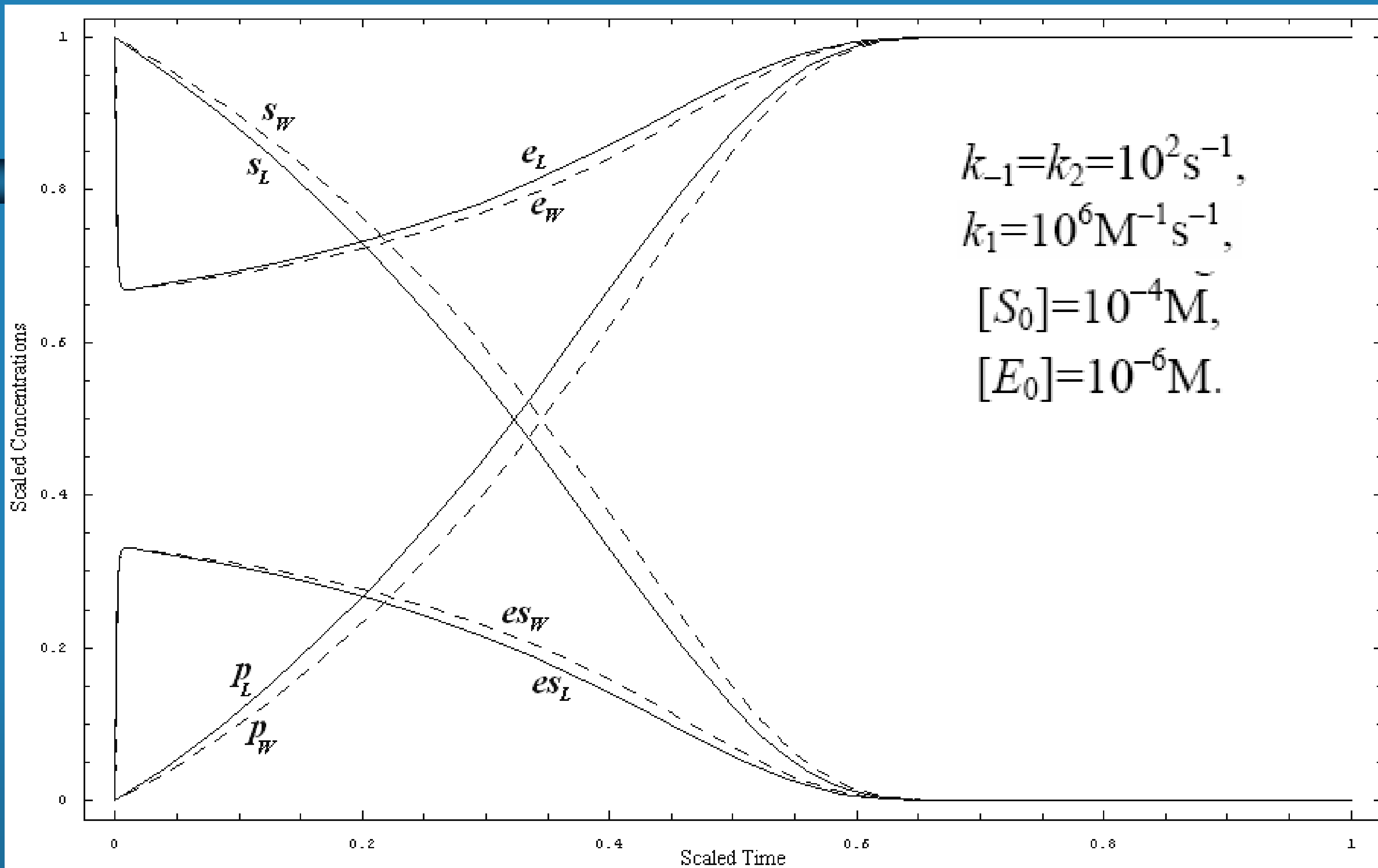
$$[ES]_{W,L}(t)=\frac{[E_0][S]_{W,L}(t)}{[S]_{W,L}(t)+K_M}\{1-\exp[-k_1 t([S_0]+K_M)]\}\ ,$$

$$[P]_{W,L}(t)=[S_0]-[S]_{W,L}(t)-[ES]_{W,L}(t)\,,$$

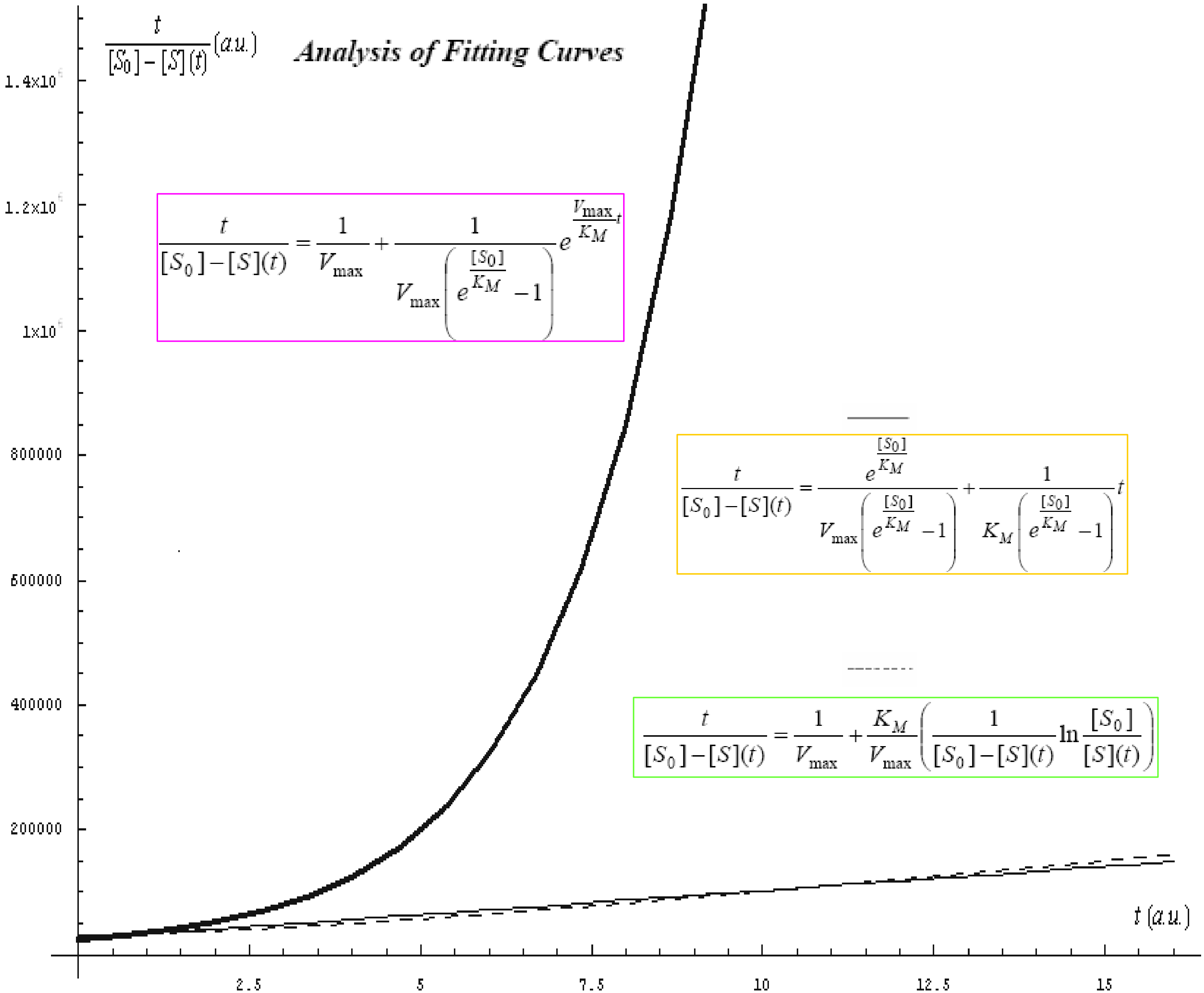
$$[E]_{W,L}(t)=[E_0]-[ES]_{W,L}(t)\,,$$

$$s_{W,L}(t)=\frac{[S]_{W,L}(t)}{[S_0]},e_{W,L}(t)=\frac{[E]_{W,L}(t)}{[E_0]},es_{W,L}(t)=\frac{[ES]_{W,L}(t)}{[E_0]},p_{W,L}(t)=\frac{[P]_{W,L}(t)}{[S_0]}$$

$$\tau=1-\frac{1}{\ln(t+\mathrm{e})}$$



Analysis of Fitting Curves



REVERSIBLE ENZYME KINETICS

$$E + S \underset{k_{-1}}{\overset{k_1}{\leftrightarrow}} ES = EP \underset{k_{-2}}{\overset{k_2}{\leftrightarrow}} E + P$$

$$0 = \frac{d}{dt}[ES] = k_1[E][S] + k_{-2}[P][E] - (k_{-1} + k_2)[ES]$$

$$[E_0] = [E] + [ES]$$

$$v = \frac{d}{dt}[P] = -\left(\frac{d}{dt}[S]\right) = -(k_{-1}[ES] - k_1[S][E])$$

$$v = \frac{k_1 k_2 [S] - k_{-1} k_{-2} [P]}{k_{-1} + k_2 + k_1[S] + k_{-2}[P]}[E_0]$$

$$K_M^S = \frac{k_{-1} + k_2}{k_1} \quad K_M^P = \frac{k_{-1} + k_2}{k_{-2}} \quad V_{\max}^f = k_2[E_0] \quad V_{\max}^r = k_{-1}[E_0]$$

$$v = \frac{V_{\max}^f \frac{[S]}{K_M^S} - V_{\max}^r \frac{[P]}{K_M^P}}{1 + \frac{[S]}{K_M^S} + \frac{[P]}{K_M^P}}$$

Michaelis-Menten version

$$k_{-2} = 0$$

W-LAMBERT SOLUTION OF REVERSIBLE ENZYME KINETICS

$$[P](t) = [P_0] + [S_0] - [S](t)$$

$$-\frac{d}{dt}[S](t) \equiv \frac{V[S](t) - R}{[S](t) + K}$$

$$V = \frac{\dfrac{V_{\max}^{f}}{K_M^S} + \dfrac{V_{\max}^{r}}{K_M^P}}{\dfrac{1}{K_M^S} - \dfrac{1}{K_M^P}} \qquad R = \frac{[P_0] + [S_0]}{\dfrac{1}{K_M^S} - \dfrac{1}{K_M^P}} \frac{V_{\max}^{r}}{K_M^P} \qquad K = \frac{1 + \dfrac{[S_0] + [P_0]}{K_M^P}}{\dfrac{1}{K_M^S} - \dfrac{1}{K_M^P}}$$

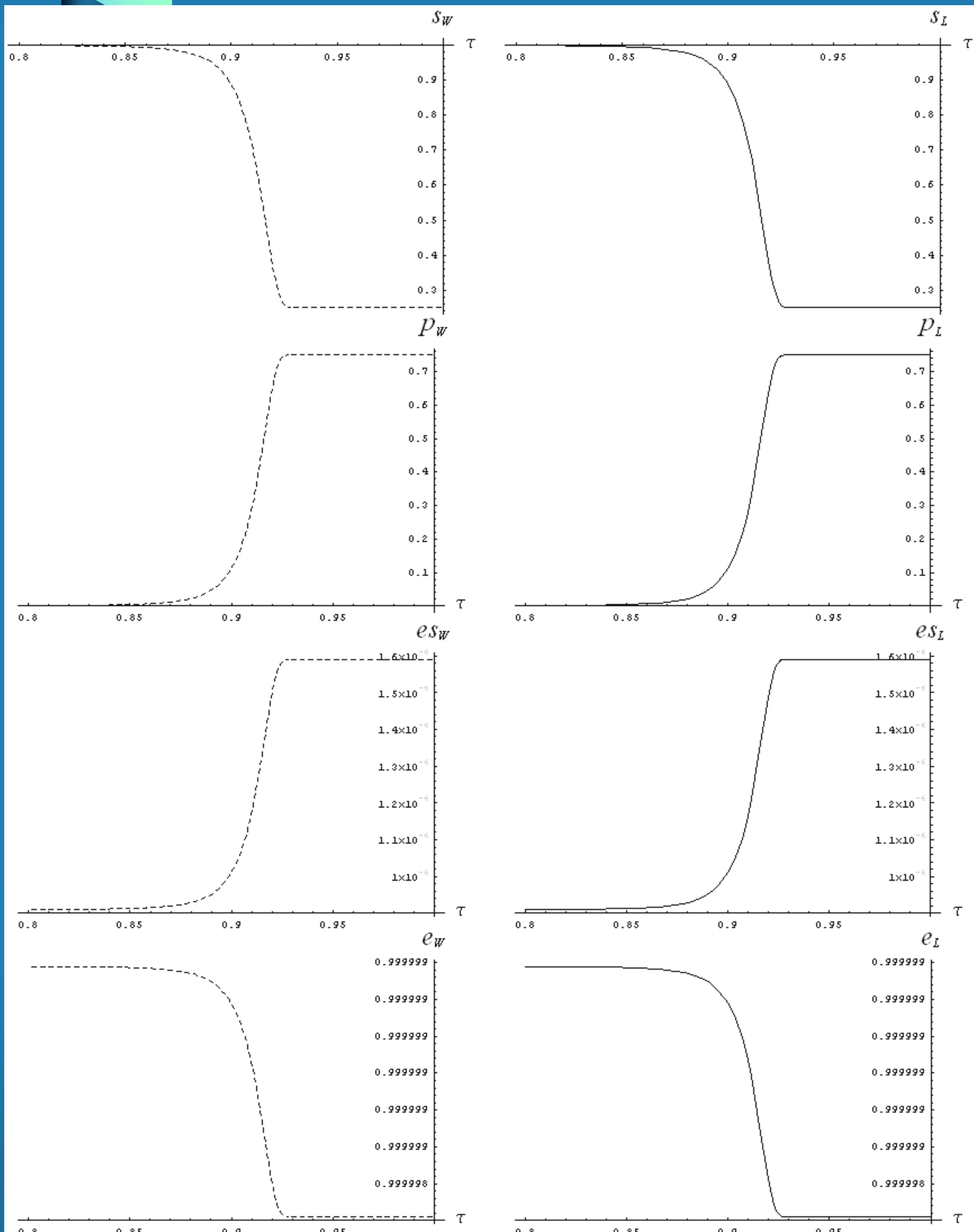
$$-t = \frac{1}{V} \int_{[S_0]}^{[S]} \frac{[S] + K}{[S] - R/V} d[S] \qquad \int \frac{x+a}{x+b} dx = x + (a-b)\ln(x+b) + ct.$$

$$-tV = [S] - [S_0] + \left(K + \frac{R}{V}\right)\left[\ln\left([S] - \frac{R}{V}\right) - \ln\left([S_0] - \frac{R}{V}\right)\right]$$

$$\frac{[S] - \dfrac{R}{V}}{K + \dfrac{R}{V}} + \ln\left(\frac{[S] - \dfrac{R}{V}}{K + \dfrac{R}{V}}\right) = \frac{[S_0] - \dfrac{R}{V}}{K + \dfrac{R}{V}} + \ln\left(\frac{[S_0] - \dfrac{R}{V}}{K + \dfrac{R}{V}}\right) - \frac{Vt}{K + \dfrac{R}{V}}$$

$$[S]_W(t) = \frac{R}{V} + \left(K + \frac{R}{V}\right) W\left(\frac{[S_0] - R/V}{K + R/V} \exp\left(\frac{[S_0] - R/V - Vt}{K + R/V}\right)\right)$$

LOGISTIC SOLUTION OF REVERSIBLE ENZYME KINETICS



$$f_1 W\left(f_2 e^{f_2} e^{-f_3 t}\right) \to f_1 \ln\left[1+\left(e^{f_2}-1\right)e^{-f_3 t}\right]$$

$$[S]_L(t) = \frac{R}{V} + \left(K+\frac{R}{V}\right)\ln\left\{1+\left[\exp\left(\frac{[S_0]-R/V}{K+R/V}\right)-1\right]\exp\left(-\frac{Vt}{K+R/V}t\right)\right\}$$

$$s_{W,L}(t) = \frac{[S]_{W,L}(t)}{[S_0]}\ , \quad p_{W,L}(t) = \frac{[P]_{W,L}(t)}{[S_0]}$$

$$es_{W,L}(t) = \frac{[ES]_{W,L}(t)}{[E_0]}\ , \quad e_{W,L}(t) = \frac{[E]_{W,L}(t)}{[E_0]}$$

$$\tau = 1 - \frac{1}{\ln(t+\mathrm{e})}$$

$$k_{-1} = 100 s^{-1},$$
$$k_2 = 1000 s^{-1},$$
$$k_1 = 0.1 M^{-1} s^{-1},$$
$$k_{-2} = 0.2 M^{-1} s^{-1},$$
$$[E_0] = 10^{-4} M\ ,$$
$$[S_0] = 10^{-2} M\ ,$$
$$[P_0] = 0 M\ .$$

W-LAMBERT ENZYME KINETICS WITH COMPETITIVE INHIBITION

$$\begin{array}{ccccccccc} S & + & E & \underset{k_{-1}}{\overset{k_1}{\leftrightarrow}} & ES & \overset{k_2}{\rightarrow} & E & + & P_S \\ & & + & & & & & & \\ & & I & \underset{k_{-3}}{\overset{k_3}{\leftrightarrow}} & EI & \overset{k_4}{\rightarrow} & E & + & P_I \end{array}$$

$$K_M^S = \frac{k_{-1}+k_2}{k_1}\,,\qquad K_M^I = \frac{k_{-3}+k_4}{k_3}\,;$$

$$V_{\max}^S = k_2[E_0]\,,\qquad V_{\max}^I = k_4[E_0]\,.$$

$$\delta = \frac{V_{\max}^I K_M^S}{V_{\max}^S K_M^I}$$ the competition matrix

$$[S'_0] = \frac{[S_0]}{K_M^S},\; [S'](t) = \frac{[S](t)}{K_M^S},$$

$$[I'_0] = \frac{[I_0]}{K_M^I},\; [I'](t) = \frac{[I](t)}{K_M^I},$$

$$[S']_W(t) = (1+[I'_0])W\left(\frac{[S'_0]}{1+[I'_0]}\exp\left(\frac{[S'_0]}{1+[I'_0]}\right)\exp\left(-\frac{V_{\max}^S t}{K_M^S(1+[I'_0])}\right)\right)$$

$$[I'](t) = [I'_0]\left(\frac{[S']_W(t)}{[S'_0]}\right)^{\delta}$$

W-Lambert vs.Logistic Enzyme Kinetics with Competitive Inhibition

$$[S']_L(t) = (1+[I'_0])\ln\left(1+\left[\exp\left(\frac{[S'_0]}{1+[I'_0]}\right)-1\right]\exp\left(-\frac{V_{\max}^S t}{K_M^S(1+[I'_0])}\right)\right)$$

$$[I']_L(t) = [I'_0]\left(\frac{[S']_L(t)}{[S'_0]}\right)^{\delta}$$

$$[ES]_{W,L}(t) = \frac{[E_0][S]_{W,L}(t)}{[S]_{W,L}(t)+K_M^S\left(1+[I]_{W,L}(t)/K_M^I\right)}\left\{1-\exp\left[-k_1 t\left([S_0]+K_M^S\left(1+[I_0]/K_M^I\right)\right)\right]\right\}$$

$$[EI]_{W,L}(t) = \frac{[E_0][I]_{W,L}(t)}{[I]_{W,L}(t)+K_M^I\left(1+[S]_{W,L}(t)/K_M^S\right)}\left\{1-\exp\left[-k_3 t\left([I_0]+K_M^I\left(1+[S_0]/K_M^S\right)\right)\right]\right\}$$

$$s_{W,L}(\tau) = \frac{[S]_{W,L}(\tau)}{[S_0]},\quad i_{W,L}(\tau) = \frac{[I]_{W,L}(\tau)}{[I_0]}$$

$$es_{W,L}(\tau) = \frac{[ES]_{W,L}(\tau)}{[E_0]},\quad ei_{W,L}(\tau) = \frac{[EI]_{W,L}(\tau)}{[E_0]}$$

$$ps_{W,L}(\tau) = \frac{[P_S]_{W,L}(\tau)}{[S_0]},\quad pi_{W,L}(\tau) = \frac{[P_I]_{W,L}(\tau)}{[I_0]}$$

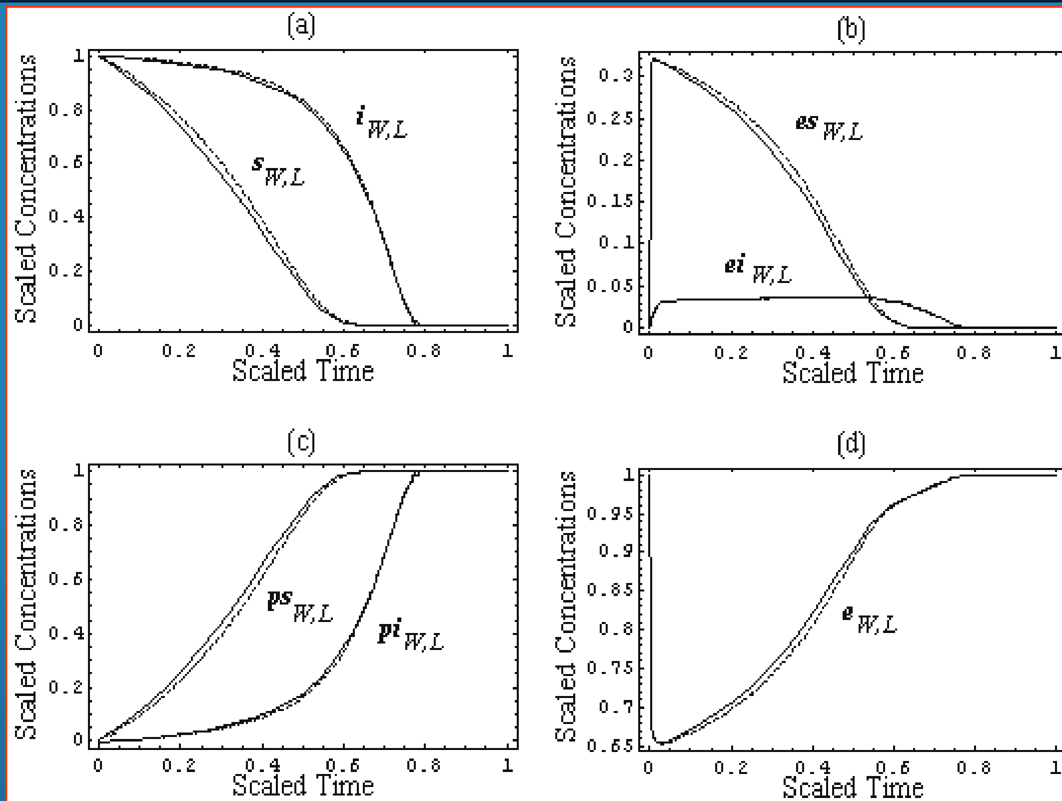
$$e_{W,L}(\tau) = \frac{[E]_{W,L}(\tau)}{[E_0]}$$

$$[P_S]_{W,L}(t) = [S_0]-[S]_{W,L}(t)-[ES]_{W,L}(t)$$

$$[P_I]_{W,L}(t) = [I_0]-[I]_{W,L}(t)-[EI]_{W,L}(t)$$

$$[E]_{W,L}(t) = [E_0]-[ES]_{W,L}(t)-[EI]_{W,L}(t)$$

$k_{-1}=k_2=10^2\,s^{-1}$, $k_1=10^6\,M^{-1}s^{-1}$,
$k_{-3}=k_4=10\,s^{-1}$, $k_3=10^5\,M^{-1}s^{-1}$,
$[S_0]=10^{-4}\,M$, $[I_0]=10^{-5}\,M$,
$[E_0]=10^{-6}\,M$



ENZYME KINETICS WITH MIXED INHIBITION

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

$$E + I \overset{K_I}{\rightleftharpoons} EI$$

$$ES + I \overset{K_{IS}}{\rightleftharpoons} ESI$$

$$K_I = \frac{[E][I]_0}{[EI]}$$

$$K_{IS} = \frac{[ES][I]_0}{[ESI]}$$

$$\alpha = 1 + \frac{[I]_0}{K_I}$$

$$\alpha' = 1 + \frac{[I]_0}{K_{IS}}$$

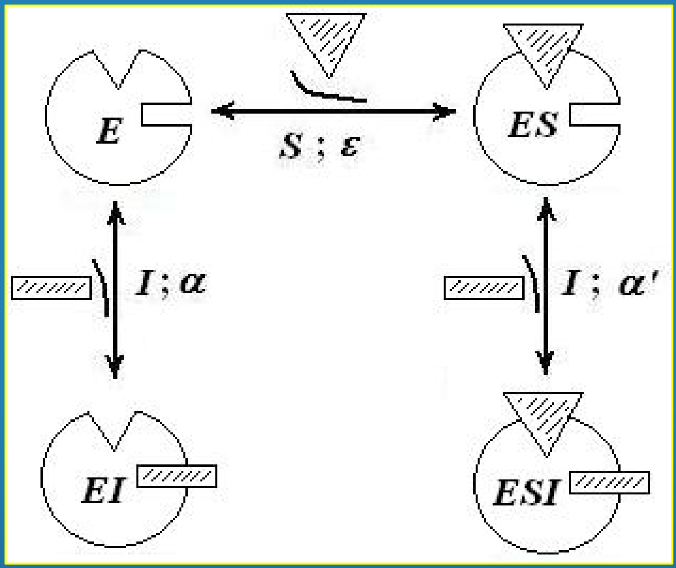
$$V_{max}^{mixed} = (1/\alpha')V_{max}^{mono}$$

$$K_M^{mixed} = (\alpha/\alpha')/K_M^{mono}$$

$$[S]_0 = \varepsilon^{-1}[E]_0 \ , \ \varepsilon < 10^{-2}$$

$$[S](t)^W = \frac{\alpha}{\alpha'} K_M W\left(\frac{\alpha'[E]_0}{\alpha\varepsilon K_M}\exp\left(\frac{\alpha'[E]_0}{\alpha\varepsilon K_M}\right)\exp\left(-\frac{tV_{max}}{\alpha K_M}\right)\right)$$

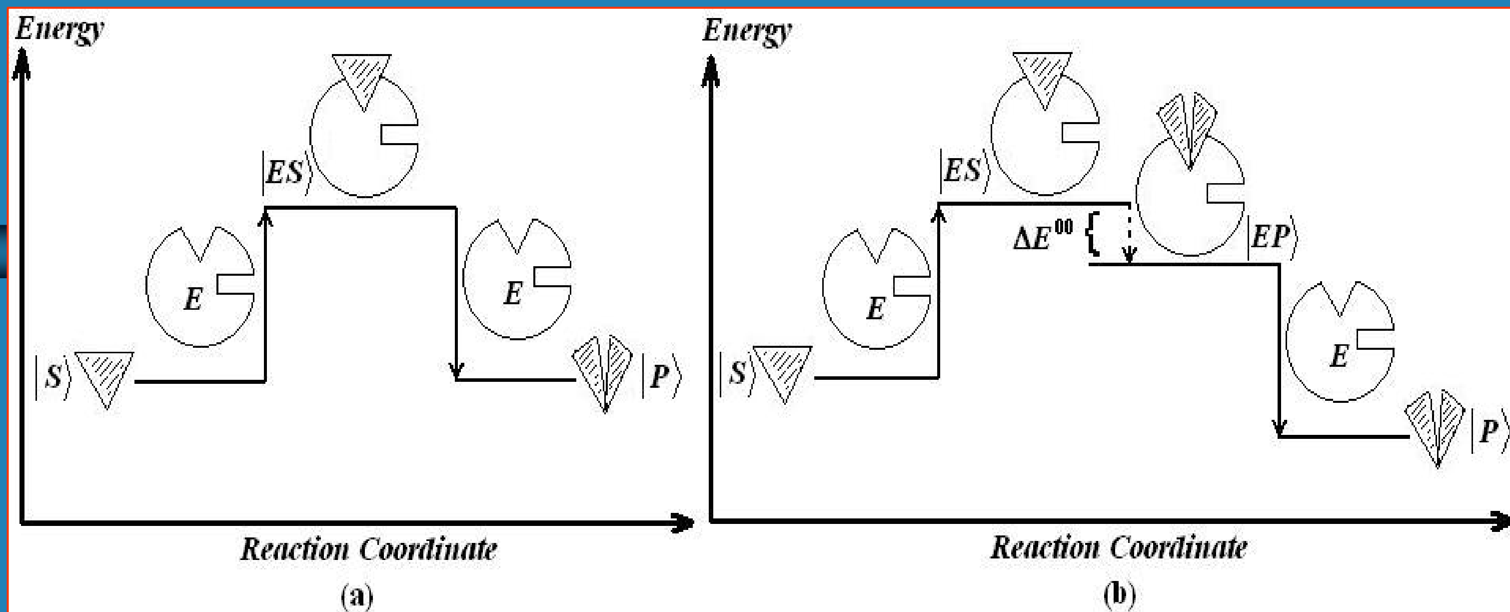
$$[S]^{Log}(t) = \frac{\alpha}{\alpha'} K_M \ln\left[1 + \left(\exp\left(\frac{\alpha'[E]_0}{\alpha\varepsilon K_M}\right) - 1\right)\exp\left(-\frac{V_{max}}{\alpha K_M}t\right)\right]$$



"THE ENZYMATIC PARADOX"

$E+S \to ES \to E+P$

$E+S \to ES \xrightarrow{delay} EP \to E+P$



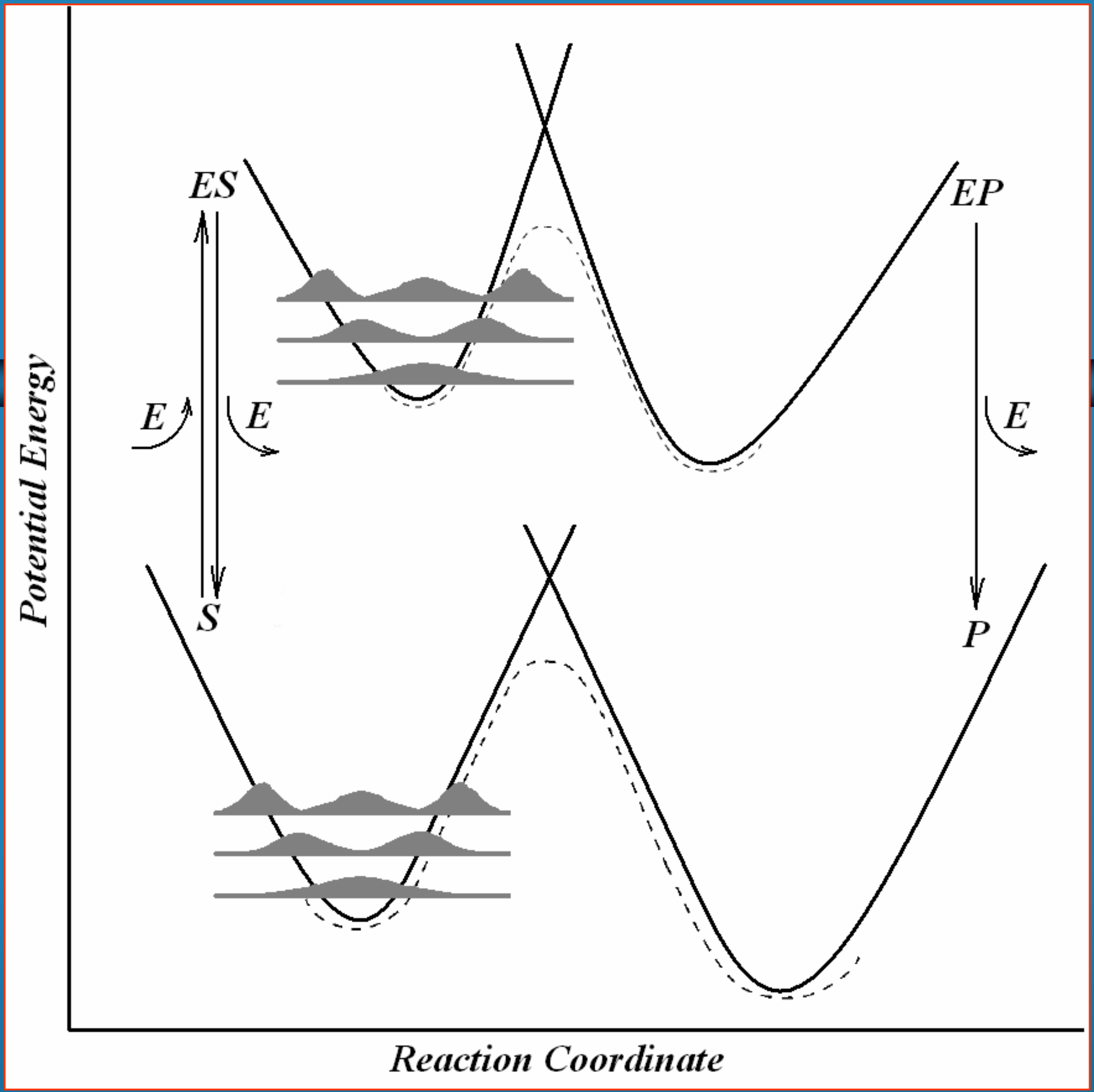
the intra-conversion of $|ES\rangle$ into $|EP\rangle$

absorption-emission process

the "photon role"

the enzyme

TUNNELING Picture of Enzyme Kinetics



ENZYMIC BEER-LAMBERT LAW

the absorbance of the substrate molecules (at a particular wavelength)

$$A_S(t) = a_M l [S](t)$$

considering the free substrate absorption

$$A_0 = a_M l [S]_0$$

we can deal, for convenience, with the normal absorptivity

$$a_S(t) = \frac{A_S(t)}{A_0} = \frac{[S](t)}{[S]_0} \qquad a_P(t) = \frac{A_P(t)}{A_0} = \frac{[P](t)}{[S]_0}$$

$$[S]_0 = [S](t) + [ES](t) + [P](t)$$

$$[E]_0 = [E](t) + [ES](t)$$

the Michaelis-Menten constant viewed as the dynamic dissociation constant

$$K_M = \frac{[E](t)[S](t)}{[ES](t)}$$

$$a_P(t) = 1 - a_S(t) - \frac{\varepsilon [S](t)}{[S](t) + K_M}, \; 10^{-7} < \varepsilon \equiv \frac{[E]_0}{[S]_0} < 10^{-2}$$

While the parameter ε fixes the in vivo to in vitro regimes as it decreases to zero the product's normal absorbance can be approximated as

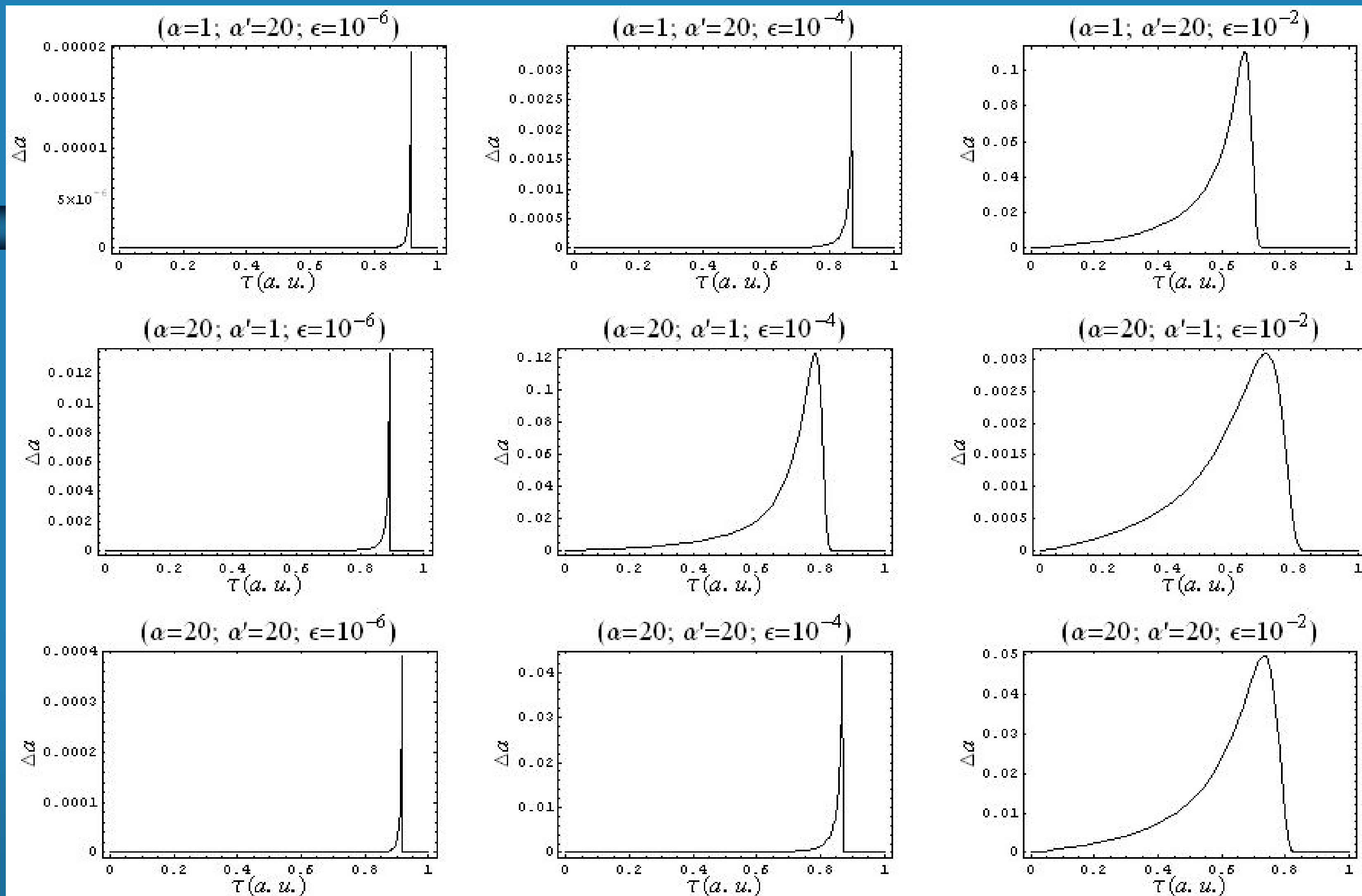
$$a_P(t) \cong 1 - a_S(t)$$

Enzymic Kinetics by W-Lambert vs. Logistic Difference Absorption with Inhibition

$$\Delta a(t) = a_S^W(t) - a_S^{Log}(t) \cong a_P^{Log}(t) - a_P^W(t)$$

in vitro, when $\varepsilon \in (10^{-6}, 10^{-4})$

vivo conditions, when $\varepsilon \geq 10^{-2}$



Enzymic Kinetics by W-Lambert vs. Logistic Difference Absorption without Inhibition

$$\Delta a(t) = a_S^{W}(t) - a_S^{Log}(t) \cong a_P^{Log}(t) - a_P^{W}(t)$$

in vitro, when $\varepsilon \in (10^{-6}, 10^{-4})$

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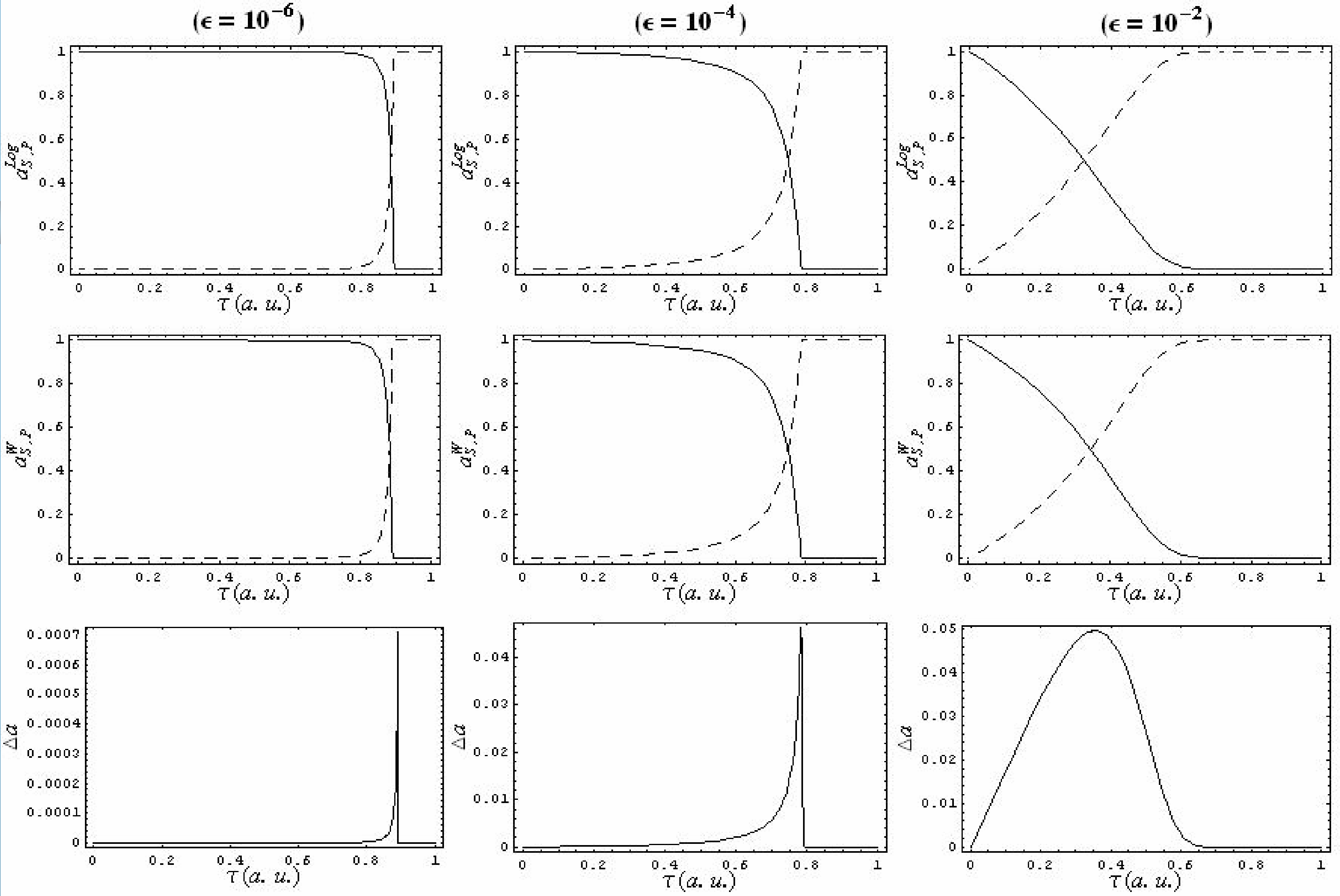


QUANTUM Information from Enzyme Kinetics Absorption

no inhibition (00)

competitive (α0)

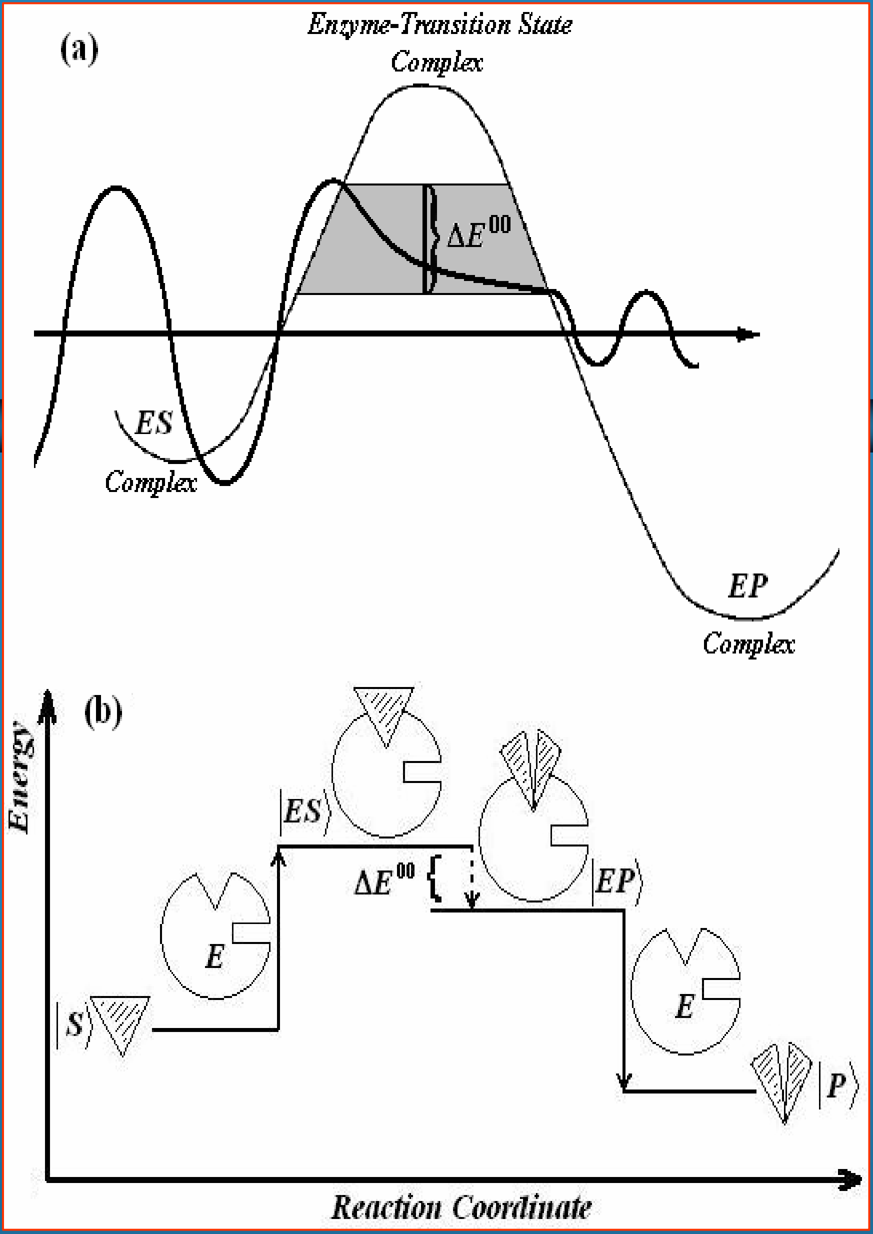
uncompetitive (0α')

mixed (αα')

$$\frac{1}{k_{cat}} \propto \Delta t \cong \frac{\hbar}{\Delta E_{tunnelling}} = \frac{\hbar}{k_B T}$$

$$\Delta\tau^{0\alpha'} < \Delta\tau^{\alpha\alpha'} < \Delta\tau^{00} < \Delta\tau^{\alpha 0},\ \varepsilon \in \left(10^{-6}, 10^{-4}\right),$$
$$\Delta\tau^{\alpha 0} < \Delta\tau^{\alpha\alpha'} < \Delta\tau^{00} < \Delta\tau^{0\alpha'},\ \varepsilon \geq 10^{-2},$$

$$\Delta E^{0\alpha'} > \Delta E^{\alpha\alpha'} > \Delta E^{00} > \Delta E^{\alpha 0},\ \varepsilon \in \left(10^{-6}, 10^{-4}\right),$$
$$\Delta E^{\alpha 0} > \Delta E^{\alpha\alpha'} > \Delta E^{00} > \Delta E^{0\alpha'},\ \varepsilon \geq 10^{-2}.$$



QUANTUM Rules for Enzyme Kinetics

(i) the enzyme assume the "photon role", as before, since as a catalysis enters and outs unaffected, i.e. caring the same amount of energy in and out of the reaction;

(ii) all other involved molecular complexes, including intermediates, are considered in their ground state and represented by their Dirac-ket vector $|\bullet\rangle$;

(iii) the non inhibited transition state $|ES\rangle$ is always placed between inhibited intermediary complexes, $|EI\rangle$ and $|ESI\rangle$;

(iv) the energy of inhibitor state $|I\rangle$ is presumably higher in vivo than in vitro, as compared with the energy level of substrate $|S\rangle$, due to the crowding of the in vivo environment.

(v) competitive inhibition is firstly considered, due to the direct attack on the enzyme;

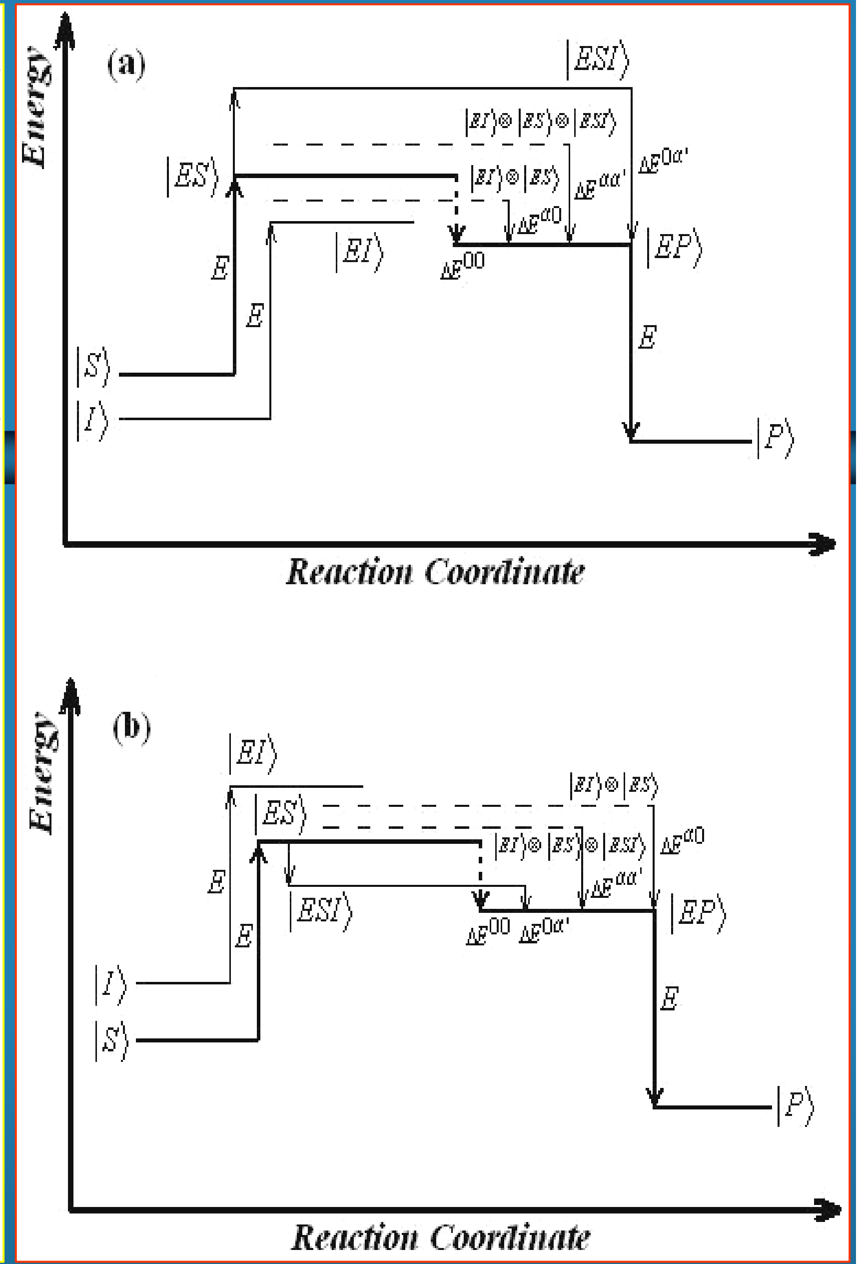
(vi) consequently, the states $|EI\rangle$ and $|ES\rangle$ are coexisting and undergo quantum combination in a mixed new intermediary state $|EI\rangle \otimes |ES\rangle$;

(vii) the uncompetitive inhibited state $|ESI\rangle$ is obtained from the state $|ES\rangle$ so that the (iii) rule above is complied with;

(viii) when both competitive $|EI\rangle \otimes |ES\rangle$ and uncompetitive $|ESI\rangle$ states are present, they further combine and the new mixed intermediary quantum $|EI\rangle \otimes |ES\rangle \otimes |ESI\rangle$ state arises, which always has to lay above the $|ES\rangle$ one;

(ix) all new inhibited intermediary states decay on the same $|EP\rangle$ state as in the case of no-inhibition (00).

(x) it follows that the energetic differences as compared with the no-inhibition case are due to the tunnelling induced by the inhibited transition states which regulate the delayed times of mixed catalysis.



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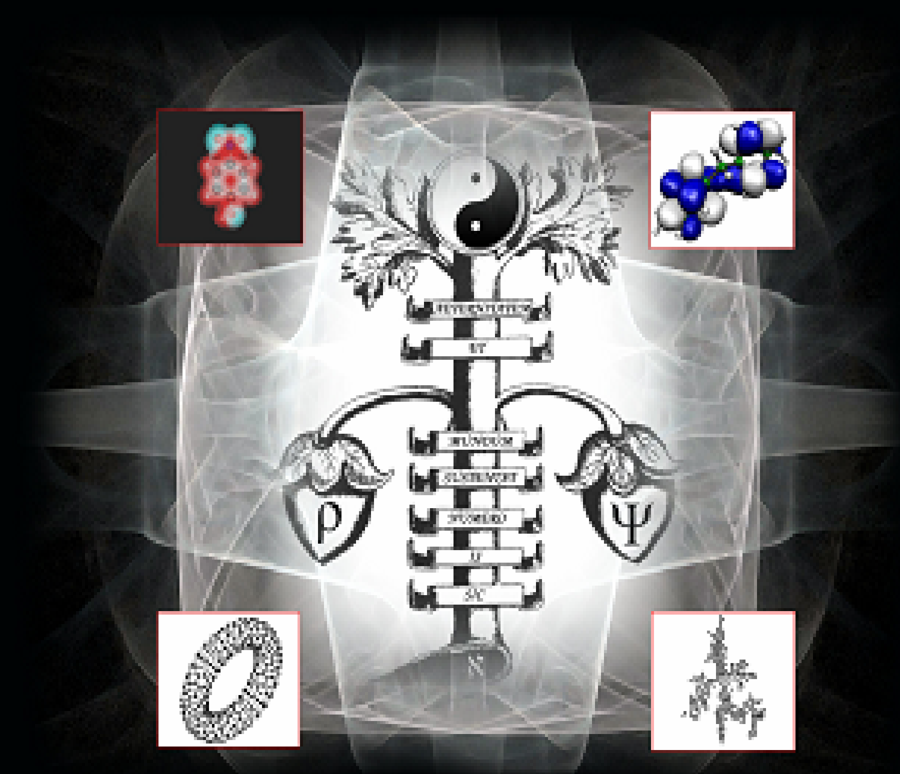

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