Substrate Inhibition.
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Mechanism. Enzyme combines with a substrate molecule for form a complex, which leads to product. The active enzyme complex ES can further combine with a substrate molecule S to form an inactive form ESS, which does not lead to product. This is described schematically as follows.

$$S + E \underset{k_i}{\overset{k_1}{\longleftrightarrow}} ES \xrightarrow{k_2} P + E$$

$$ES + S \; \underset{k_4}{\overset{k_3}{\downarrow\uparrow}} \; ESS \text{ (inactive)}$$

The 2nd part is equivalent to the following notation.

$$ES + S \underset{k_4}{\overset{k_3}{\longleftrightarrow}} ESS$$

Derivation of Reaction Rate Expression with Equilibrium Assumption.

Given

1. dp/dt=rate=v $\qquad v = k_2 \cdot ES$
2. Conservation of enzyme species $\qquad E_0 = E + ES + ESS$
3. Equilibrium Assumption: $\qquad k_1 \cdot S \cdot E = k_i \cdot ES \qquad k_3 \cdot S \cdot ES = k_4 \cdot ESS$

We have 4 eqns, and we can choose to solve for any of the four unknowns -- E, ES, ESS, and v)
Find the analytical expression (via |Math|SmartMath|)

$$\mathrm{Find}(E, ES, ESS, v) \rightarrow \begin{bmatrix} E_0 \cdot k_4 \cdot \dfrac{k_i}{\left(k_4 \cdot k_1 \cdot S + k_4 \cdot k_i + k_1 \cdot S^2 \cdot k_3\right)} \\ \dfrac{1}{\left(k_4 \cdot k_1 \cdot S + k_4 \cdot k_i + k_1 \cdot S^2 \cdot k_3\right)} \cdot k_4 \cdot k_1 \cdot S \cdot E_0 \\ k_3 \cdot \dfrac{S^2}{\left(k_4 \cdot k_1 \cdot S + k_4 \cdot k_i + k_1 \cdot S^2 \cdot k_3\right)} \cdot k_1 \cdot E_0 \\ \dfrac{k_2}{\left(k_4 \cdot k_1 \cdot S + k_4 \cdot k_i + k_1 \cdot S^2 \cdot k_3\right)} \cdot k_4 \cdot k_1 \cdot S \cdot E_0 \end{bmatrix}$$

Thus, the last row is the analytical expression for v.

$$v = \frac{k_2}{\left(k_1 \cdot S \cdot k_4 + k_4 \cdot k_i + S^2 \cdot k_3 \cdot k_1\right)} \cdot k_4 \cdot k_1 \cdot S \cdot E_0$$

Thus, the above form is transformed into the Michaelis-Menten form by defining:

$$v_m = k_2 \cdot E_0 \qquad K_m = \frac{k_i}{k_1} \qquad K_i = \frac{k_4}{k_3}$$

$$v(s) = \frac{v_m \cdot s}{K_m + s + \dfrac{s^2}{K_i}}$$

Derivation of Reaction Rate Expression with the Quasi-Steady State Assumption.

Given

1. dp/dt=rate=v $\quad v = k_2 \cdot ES$

2. Conservation of enzyme species $\quad E_0 = E + ES + ESS$

3. Quasi-Steady State Assumption (applicable to the intermediate species ES_1 and ES_2):

d ES/dt = 0 $\quad k_1 \cdot S \cdot E - k_i \cdot ES - k_2 \cdot ES - k_3 \cdot S \cdot ES + k_4 \cdot ESS = 0$

d ESS/dt = 0 $\quad k_3 \cdot S \cdot ES - k_4 \cdot ESS = 0$

(Our work is done, just let Mathcad do the rest.) Find the analytical expression (via |Math|SmartMath|)

$$\mathrm{Find}(E, ES, ESS, v) \rightarrow \begin{bmatrix} E_0 \cdot k_4 \cdot \dfrac{(k_i + k_2)}{(k_4 \cdot k_1 \cdot S + k_4 \cdot k_i + k_4 \cdot k_2 + k_1 \cdot S^2 \cdot k_3)} \\ \dfrac{1}{(k_4 \cdot k_1 \cdot S + k_4 \cdot k_i + k_4 \cdot k_2 + k_1 \cdot S^2 \cdot k_3)} \cdot k_4 \cdot k_1 \cdot S \cdot E_0 \\ k_3 \cdot \dfrac{S^2}{(k_4 \cdot k_1 \cdot S + k_4 \cdot k_i + k_4 \cdot k_2 + k_1 \cdot S^2 \cdot k_3)} \cdot k_1 \cdot E_0 \\ \dfrac{k_2}{(k_4 \cdot k_1 \cdot S + k_4 \cdot k_i + k_4 \cdot k_2 + k_1 \cdot S^2 \cdot k_3)} \cdot k_4 \cdot k_1 \cdot S \cdot E_0 \end{bmatrix}$$

Thus, the last row is the analytical expression for v (although it does not look very compact).

$$v = \frac{k_2}{(k_4 \cdot k_1 \cdot S + k_4 \cdot k_i + k_4 \cdot k_2 + k_1 \cdot S^2 \cdot k_3)} \cdot k_4 \cdot k_1 \cdot S \cdot E_0$$

Thus, the above form is transformed into the Michaelis-Menten form by defining:

$$v_m = k_2 \cdot E_0 \qquad K_m = \frac{k_i + k_2}{k_1} \qquad K_i = \frac{k_4}{k_3}$$

$$v = \frac{v_m \cdot s}{K_m + s + \dfrac{s^2}{K_i}}$$

The reaction rate expression shows **substrate inhibition**.

Calculation of the Maximum Point. The rate goes through a maximum when **dv/ds=0**. Let's find where this maximum lies. Here, we mark "s" in the above equation and choose |Symbolic|Differentiate on Variable|.

$$0=\frac{v_m}{\left(K_m+s+\frac{s^2}{K_i}\right)}-v_m\cdot\frac{s}{\left(K_m+s+\frac{s^2}{K_i}\right)^2}\cdot\left(1+2\cdot\frac{s}{K_i}\right)$$

Choose |Symbolic|Simplify| yields:

$$0=v_m\cdot K_i\cdot\frac{\left(K_m\cdot K_i-s^2\right)}{\left(K_m\cdot K_i+s\cdot K_i+s^2\right)^2}$$

Since there is only one equation, mark "s" in the above equation and choose |Symbolic|Solve for Variable| yields:

$$\begin{bmatrix}-\sqrt{K_m}\cdot\sqrt{K_i}\\ \sqrt{K_m}\cdot\sqrt{K_i}\end{bmatrix}$$

Since the substrate concentration must be non-negative, we choose the second solution.

$$s_{max}=\sqrt{K_m\cdot K_i}$$

Finally, the maximum rate is $v_{max}=v(s_{max})$

$$v_{max}=\frac{v_m\cdot s_{max}}{K_m+s_{max}+\frac{s_{max}^2}{K_i}}$$

Copy "$\sqrt{K_m\cdot K_i}$" into the clipboard, mark "s_{max}" in the last equation, and choose |Symbolic|Substitute for Variable| yields:

$$v_{max}=v_m\cdot\sqrt{K_i}\cdot\frac{\sqrt{K_m}}{\left(2\cdot K_m+\sqrt{K_m}\cdot\sqrt{K_i}\right)}$$

Further choosing |Symbolic|Simplify| yields:

$$v_{max}=\frac{v_m\cdot\sqrt{K_i}}{2\cdot\sqrt{K_m}+\sqrt{K_i}}$$

Alternately, we can find v_{max} by solving the following two equations simultaneously.

Given $s_{max} = \sqrt{K_m \cdot K_i}$ $v_{max} = \dfrac{v_m \cdot s_{max}}{K_m + s_{max} + \dfrac{s_{max}^2}{K_i}}$

$$\mathrm{Find}(s_{max}, v_{max}) \rightarrow \begin{bmatrix} \sqrt{K_m} \cdot \sqrt{K_i} \\ v_m \cdot \sqrt{K_m} \cdot \dfrac{K_i^{\left(\frac{3}{2}\right)}}{\left[2 \cdot K_m \cdot K_i + \sqrt{K_m} \cdot K_i^{\left(\frac{3}{2}\right)}\right]} \end{bmatrix}$$

v_{max} is the second element in the above solution vector -- copy and paste it.

$$v_{max} = v_m \cdot \sqrt{K_m} \cdot \frac{K_i^{\left(\frac{3}{2}\right)}}{\left[2 \cdot K_m \cdot K_i + \sqrt{K_m} \cdot K_i^{\left(\frac{3}{2}\right)}\right]}$$

Choose |Symbolic|Simplify| yields the same answer as before (as it should be).

$$v_{max} = \frac{v_m \cdot \sqrt{K_i}}{2 \cdot \sqrt{K_m} + \sqrt{K_i}}$$

Half-Maximum Calculation. There are two points at which $v = \frac{1}{2} \cdot v_{max}$

$$\frac{v_m \cdot s}{K_m + s + \frac{s^2}{K_i}} = \frac{1}{2} \cdot \frac{v_m \cdot \sqrt{K_i}}{2 \cdot \sqrt{K_m} + \sqrt{K_i}}$$

Since there is only one equation, mark "s" and choose |Symbolic|Solve for Variable| yields:

$$\begin{bmatrix} \frac{-1}{\left(2 \cdot \sqrt{K_i}\right)} \cdot \left[-4 \cdot K_i \cdot \sqrt{K_m} - K_i^{\left(\frac{3}{2}\right)} + \sqrt{12 \cdot K_i^2 \cdot K_m + 8 \cdot K_i^{\left(\frac{5}{2}\right)} \cdot \sqrt{K_m} + K_i^3} \right] \\ \frac{-1}{\left(2 \cdot \sqrt{K_i}\right)} \cdot \left[-4 \cdot K_i \cdot \sqrt{K_m} - K_i^{\left(\frac{3}{2}\right)} - \sqrt{12 \cdot K_i^2 \cdot K_m + 8 \cdot K_i^{\left(\frac{5}{2}\right)} \cdot \sqrt{K_m} + K_i^3} \right] \end{bmatrix}$$

Alternately, we can call |Math|SmartMath|. This method works when there are multiple equations.
(Of course, it works for just one equation, as well.)

Given $$\frac{v_m \cdot s}{K_m + s + \frac{s^2}{K_i}} = \frac{1}{2} \cdot \frac{v_m \cdot \sqrt{K_i}}{2 \cdot \sqrt{K_m} + \sqrt{K_i}}$$

$$\mathrm{Find}(s) \rightarrow \left[\frac{1}{\left(2 \cdot \sqrt{K_i}\right)} \cdot \left[4 \cdot K_i \cdot \sqrt{K_m} + K_i^{\left(\frac{3}{2}\right)} + \sqrt{12 \cdot K_i^2 \cdot K_m + 8 \cdot K_i^{\left(\frac{5}{2}\right)} \cdot \sqrt{K_m} + K_i^3} \right] \quad \frac{1}{\left(2 \cdot \sqrt{K_i}\right)} \cdot \left[4 \cdot K_i \cdot \sqrt{K_m} + K_i^{\left(\frac{3}{2}\right)} - \sqrt{12 \cdot K \right.\right.$$

Copy each term out and choose |Symboli|Simplify| yields the following two substrate concentrations:

$$s_1 = \frac{-1}{2} \cdot \sqrt{K_i} \cdot \left(-4 \cdot \sqrt{K_m} - \sqrt{K_i} + \sqrt{12 \cdot K_m + 8 \cdot \sqrt{K_m} \cdot \sqrt{K_i} + K_i} \right)$$

$$s_2 = \frac{1}{2} \cdot \sqrt{K_i} \cdot \left(4 \cdot \sqrt{K_m} + \sqrt{K_i} + \sqrt{12 \cdot K_m + 8 \cdot \sqrt{K_m} \cdot \sqrt{K_i} + K_i} \right)$$

Numerical Plot of Substrate Inhibition Rate Expression

Model parameters

$v_m := 1 \qquad K_m := 1 \qquad K_i := 1$

Substrate inhibition rate expression

$$v(s) := \frac{v_m \cdot s}{K_m + s + \dfrac{s^2}{K_i}}$$

Maximum values

$$s_{max} := \sqrt{K_m \cdot K_i} \qquad v_{max} := \frac{v_m \cdot \sqrt{K_i}}{2 \cdot \sqrt{K_m} + \sqrt{K_i}}$$

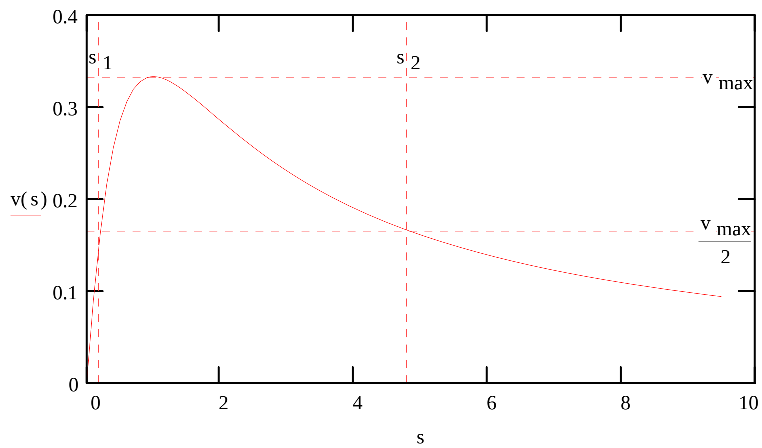
$$s_{max} = 1 \qquad v_{max} = 0.333$$

Half-maximum values

$$s_1 := \frac{-1}{2} \cdot \sqrt{K_i} \cdot \left(-4 \cdot \sqrt{K_m} - \sqrt{K_i} + \sqrt{12 \cdot K_m + 8 \cdot \sqrt{K_m} \cdot \sqrt{K_i} + K_i}\right) \qquad s_1 = 0.209$$

$$s_2 := \frac{1}{2} \cdot \sqrt{K_i} \cdot \left(4 \cdot \sqrt{K_m} + \sqrt{K_i} + \sqrt{12 \cdot K_m + 8 \cdot \sqrt{K_m} \cdot \sqrt{K_i} + K_i}\right) \qquad s_2 = 4.791$$

Plot for s ranging over $s := 0, 0.1 .. 2 \cdot s_2$



Note that purely numerical calculation is much more abbreviated -- pages of symbolic derivation is reduced to just the next few lines.

$s := 0$ ... initial guess

Maximum point: Given $\frac{d}{ds} v(s) = 0 \qquad s_{max} := \text{Find}(s) \qquad s_{max} = 1$

☹ Mathcad v7 fails to find a solution with the "Given-Find" block, but "root" is o.k.

$$s_{max} := \text{root}\left(\frac{d}{ds} v(s), s\right) \qquad s_{max} = 0.999$$

$$v_{max} := v\left(s_{max}\right) \qquad v_{max} = 0.333$$

Half-maximum point: Given $v(s) = \frac{1}{2} \cdot v_{max} \qquad s_{half} := \text{Find}(s) \qquad s_{half} = 0.209$

Repeat with another initial guess to find the second solution. $s := 2$

Given $v(s) = \frac{1}{2} \cdot v_{max}$ $s_{half} := \text{Find}(s)$ $s_{half} = 4.791$

$$i^{2}\cdot K_{m} + 8\cdot K_{i}^{\left(\frac{5}{2}\right)}\cdot\sqrt{K_{m}} + K_{i}^{3}\Big]\Bigg]$$