Enzyme inhibition.
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Enzyme inhibition can be classified into the following three categories, depending on the mechanism.

- Competitive ... The inhibitor binds to the active site and competes with the substrate.
- Non-competitive ... The inhibitor binds to a different site and reduces enzyme activity.
- Un-competitive ... The inhibitor binds to and inactivate the enzyme-substrate complex.

Derivation of Reaction Rate Expression with Equilibrium Assumption .

1. Competitive Inhibition.

$$E + S \overset{K_m}{\longleftrightarrow} ES \overset{k_2}{\longrightarrow} E + P$$

$$E + I \overset{K_I}{\longleftrightarrow} EI \text{ (inactive)}$$

Given

1. dp/dt=rate=v $\quad v = k_2 \cdot ES$
2. Conservation of enzyme species $\quad E_0 = E + EI + ES$
3. Equilibrium Assumption: $\quad \frac{S \cdot E}{ES} = K_m \qquad \frac{E \cdot I}{EI} = K_I$

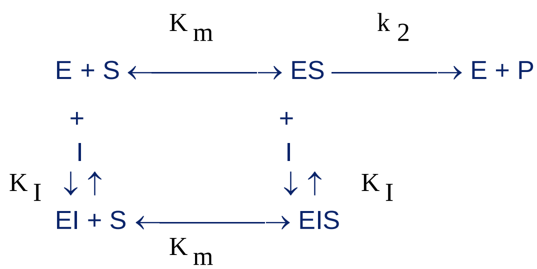
$$\text{Find}(E, EI, ES, v) \rightarrow \begin{bmatrix} K_m \cdot K_I \cdot \dfrac{E_0}{(K_m \cdot I + K_I \cdot K_m + K_I \cdot S)} \\ E_0 \cdot K_m \cdot \dfrac{I}{(K_m \cdot I + K_I \cdot K_m + K_I \cdot S)} \\ K_I \cdot E_0 \cdot \dfrac{S}{(K_m \cdot I + K_I \cdot K_m + K_I \cdot S)} \\ k_2 \cdot K_I \cdot E_0 \cdot \dfrac{S}{(K_m \cdot I + K_I \cdot K_m + K_I \cdot S)} \end{bmatrix}$$

$$v = \frac{k_2 \cdot E_0 \cdot S}{K_m \cdot \left(1 + \frac{I}{K_I}\right) + S} = \frac{v_{mapp} \cdot S}{K_{mapp} + S}$$

where $\quad v_{mapp} = k_2 \cdot E_0 = v_m \quad$ ← no change

$K_{mapp} = K_m \cdot \left(1 + \frac{I}{K_I}\right) \quad$ ← As I ↑, K_{mapp} ↑.

2. Non-competitive Inhibition.



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

2. Conservation of enzyme species $E_0 = E + EI + EIS + ES$

3. Equilibrium Assumption: $\frac{S \cdot E}{ES} = K_m$ $\frac{ES \cdot I}{EIS} = K_I$ $\frac{E \cdot I}{EI} = K_I$

$$\text{Find}(E, EI, EIS, ES, v) \rightarrow \begin{bmatrix} K_m \cdot K_I \cdot \frac{E_0}{(K_m \cdot I + K_I \cdot K_m + S \cdot I + K_I \cdot S)} \\ E_0 \cdot K_m \cdot \frac{I}{(K_m \cdot I + K_I \cdot K_m + S \cdot I + K_I \cdot S)} \\ E_0 \cdot \frac{S}{(K_m \cdot I + K_I \cdot K_m + S \cdot I + K_I \cdot S)} \cdot I \\ K_I \cdot E_0 \cdot \frac{S}{(K_m \cdot I + K_I \cdot K_m + S \cdot I + K_I \cdot S)} \\ k_2 \cdot K_I \cdot E_0 \cdot \frac{S}{(K_m \cdot I + K_I \cdot K_m + S \cdot I + K_I \cdot S)} \end{bmatrix}$$

$$v = \frac{k_2 \cdot K_I \cdot E_0 \cdot S}{K_m \cdot I + K_I \cdot K_m + S \cdot I + S \cdot K_I} = \frac{k_2 \cdot E_0 \cdot S}{\left(1 + \frac{I}{K_I}\right) \cdot (K_m + S)} = \frac{v_{mapp} \cdot S}{K_{mapp} + S}$$

where $v_{mapp} = \frac{k_2 \cdot E_0}{1 + \frac{I}{K_I}} = \frac{v_m}{1 + \frac{I}{K_I}}$ ← As I ↑, v_m ↓.

$K_{mapp} = K_m$ ← no change

3. Un-competitive Inhibition.

$$E + S \underset{}{\overset{K_m}{\longleftrightarrow}} ES \overset{k_2}{\longrightarrow} E + P$$

$$ES + I \overset{K_I}{\longleftrightarrow} ESI \text{ (inactive)}$$

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

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

3. Equilibrium Assumption: $\quad \frac{S \cdot E}{ES} = K_m \qquad \frac{ES \cdot I}{ESI} = K_I$

$$\text{Find}(E, ESI, ES, v) \rightarrow \begin{bmatrix} K_m \cdot K_I \cdot \frac{E_0}{(S \cdot I + K_I \cdot K_m + K_I \cdot S)} \\ E_0 \cdot S \cdot \frac{I}{(S \cdot I + K_I \cdot K_m + K_I \cdot S)} \\ K_I \cdot E_0 \cdot \frac{S}{(S \cdot I + K_I \cdot K_m + K_I \cdot S)} \\ k_2 \cdot K_I \cdot E_0 \cdot \frac{S}{(S \cdot I + K_I \cdot K_m + K_I \cdot S)} \end{bmatrix}$$

$$v = \frac{k_2 \cdot E_0 \cdot S}{K_m + S \cdot \left(1 + \frac{I}{K_I}\right)} = \frac{v_{mapp} \cdot S}{K_{mapp} + S}$$

where $v_{mapp} = \frac{k_2 \cdot E_0}{1 + \frac{I}{K_I}} = \frac{v_m}{1 + \frac{I}{K_I}}$ ← As I ↑, v_{mapp} ↓.

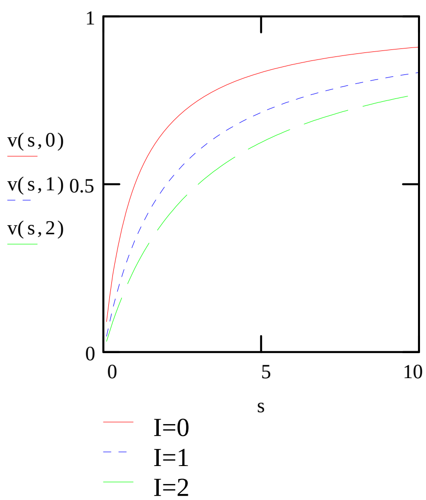
$K_{mapp} = \frac{K_m}{1 + \frac{I}{K_I}}$ ← As I ↑, K_{mapp} ↓.

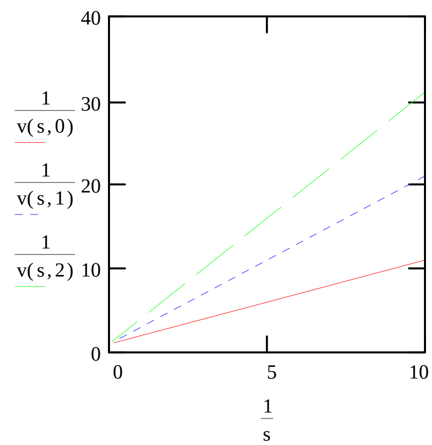
Velocity and Lineweaver-Burk Plots

1. Competitive Inhibition.

$v_m := 1 \qquad K_m := 1 \qquad K_I := 1 \qquad v(S,I) := \dfrac{v_m \cdot S}{K_m \cdot \left(1 + \dfrac{I}{K_I}\right) + S}$

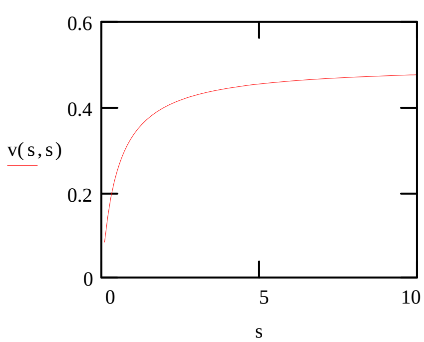
$s := 0.1, 0.2 .. 10$

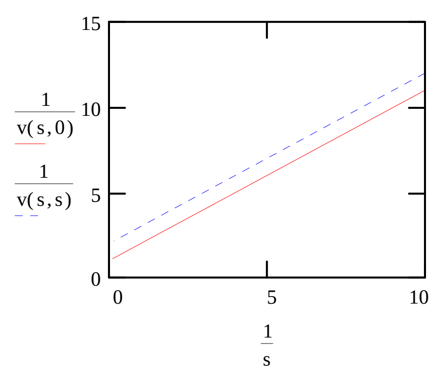




Common intercept; increased slope.

Substrate inhibition results when the inhibitor is the substrate, I=S





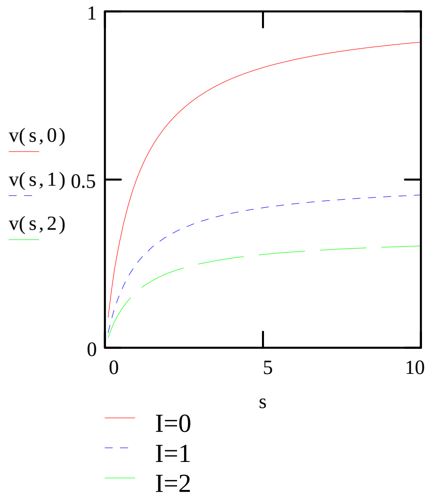
v is the same saturation curve, with reduced v_m and reduced K_m. Competitive inhibition of substrate by substrate is the same as no competitive inhibition at all; a given substrate molecule is always in competition with other substrate molecules.

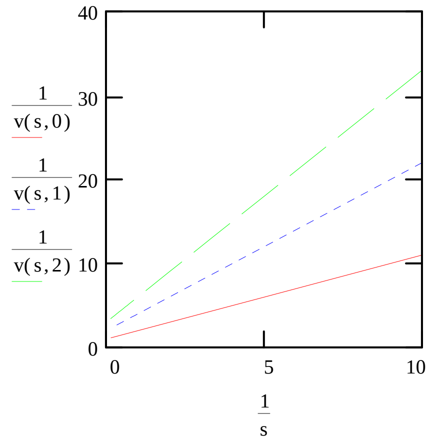
Increased intercept; common slope.

$$v = \frac{v_m \cdot S}{K_m + \left(\dfrac{K_m}{K_I} + 1\right) \cdot S} = \frac{v_{mapp} \cdot S}{K_{mapp} + S} \quad \text{where} \quad v_{mapp} = \frac{v_m}{\dfrac{K_m}{K_I} + 1} \qquad K_{mapp} = \frac{K_m}{\dfrac{K_m}{K_I} + 1}$$

2. Non-competitive Inhibition.

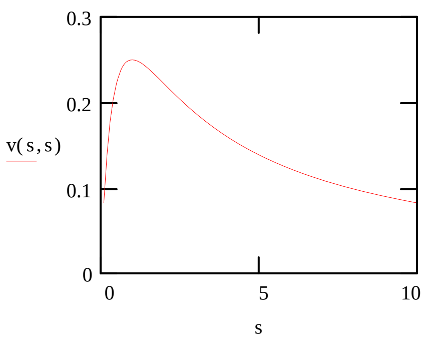
$$v(S,I) := \frac{v_m \cdot S}{\left(1 + \frac{I}{K_I}\right)\cdot\left(K_m + S\right)}$$

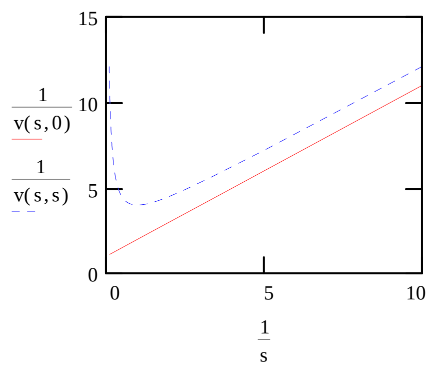




Increased intercept & slope.

Substrate inhibition results when the inhibitor is the substrate, I=S





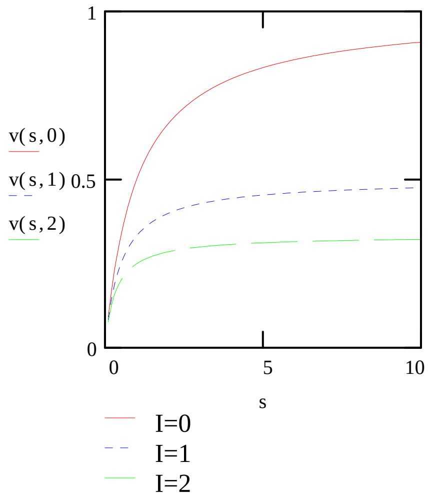
v curves downward at high value of s

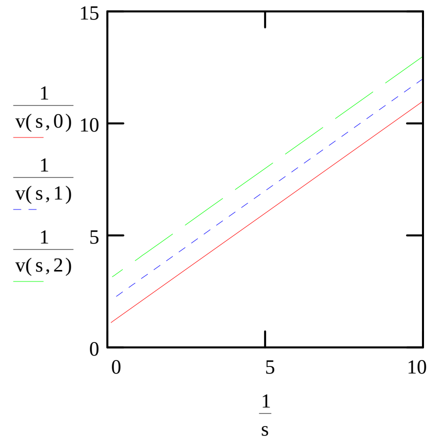
$$v = \frac{v_m \cdot S}{\left(1 + \frac{S}{K_I}\right)\cdot\left(K_m + S\right)}$$

← S term in the numerator, but quadratic S^2 term in the denominator.

3. Un-competitive Inhibition.

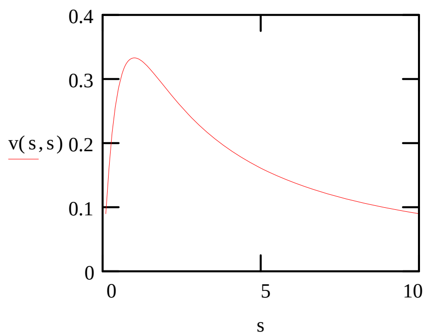
$$v(S,I) := \frac{v_m \cdot S}{K_m + S \cdot \left(1 + \frac{I}{K_I}\right)}$$

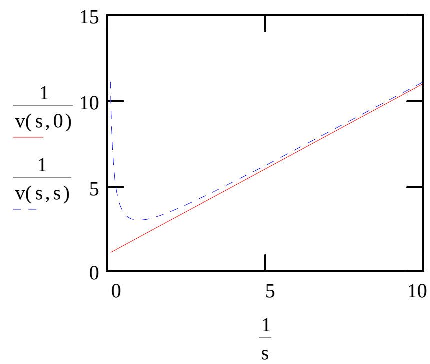




Increased intercept; common slope.

Substrate inhibition results when the inhibitor is the substrate, I=S





v curves downward at high value of s

$$v = \frac{v_m \cdot S}{K_m + S + \frac{1}{K_I} \cdot S^2}$$

← S term in the numerator, but quadratic S^2 term in the denominator. Thus, substrate inhibition via the non-competitive inhibition mechanism cannot be distinguished from that from the uncompetitive inhibition mechanism.