

Enzyme inhibition.

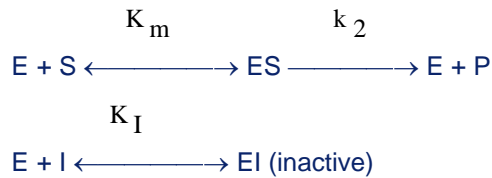
Instructor: Nam Sun Wang

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.



Given

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

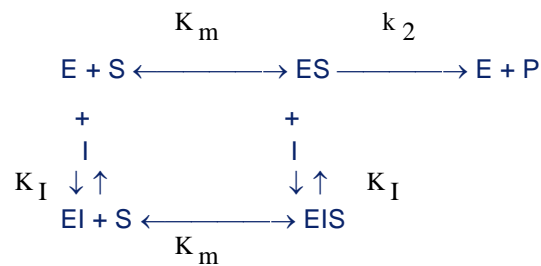
$$\text{Find}(E, EI, ES, v) \Rightarrow \left[ \begin{array}{c}
 K_m \cdot K_I \frac{E_0}{(K_m \cdot I + K_I \cdot K_m + K_I \cdot S)} \\
 E_0 \cdot K_m \frac{I}{(K_m \cdot I + K_I \cdot K_m + K_I \cdot S)} \\
 K_I \cdot E_0 \frac{S}{(K_m \cdot I + K_I \cdot K_m + K_I \cdot S)} \\
 k_2 \cdot K_I \cdot E_0 \frac{S}{(K_m \cdot I + K_I \cdot K_m + K_I \cdot S)}
 \end{array} \right]$$

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

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

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

## 2. Non-competitive Inhibition.



Given 1.  $dp/dt = \text{rate} = v$

$$v = k_2 \cdot ES$$

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

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

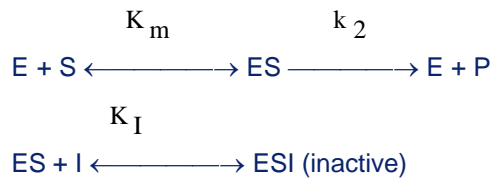
$$\text{Find}(E, EI, EIS, ES, v) \Rightarrow \left[ \begin{array}{l}
 K_m \cdot K_I \cdot \frac{E_0}{(K_m \cdot I + K_I \cdot K_m + S \cdot I + K_I \cdot S)} \\
 E_0 \cdot K_m \cdot \frac{I}{(K_m \cdot I + K_I \cdot K_m + S \cdot I + K_I \cdot S)} \\
 E_0 \cdot \frac{S}{(K_m \cdot I + K_I \cdot K_m + S \cdot I + K_I \cdot S)} \cdot I \\
 K_I \cdot E_0 \cdot \frac{S}{(K_m \cdot I + K_I \cdot K_m + S \cdot I + K_I \cdot S)} \\
 k_2 \cdot K_I \cdot E_0 \cdot \frac{S}{(K_m \cdot I + K_I \cdot K_m + S \cdot I + K_I \cdot S)}
 \end{array} \right]$$

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

$$\text{where } v_{\text{mapp}} = \frac{k_2 \cdot E_0}{1 + \frac{I}{K_I}} = \frac{v_m}{1 + \frac{I}{K_I}} \leftarrow \text{As } I \uparrow, v_m \downarrow.$$

$$K_{\text{mapp}} = K_m \quad \leftarrow \text{no change}$$

### 3. Un-competitive Inhibition.



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

$$\text{Find}(E, ESI, ES, v) \Rightarrow \left[ \begin{array}{c} E_0 \\ K_m \cdot K_I \cdot \frac{E_0}{(S \cdot I + K_I \cdot K_m + K_I \cdot S)} \\ E_0 \cdot S \cdot \frac{I}{(S \cdot I + K_I \cdot K_m + K_I \cdot S)} \\ K_I \cdot E_0 \cdot \frac{S}{(S \cdot I + K_I \cdot K_m + K_I \cdot S)} \\ k_2 \cdot K_I \cdot E_0 \cdot \frac{S}{(S \cdot I + K_I \cdot K_m + K_I \cdot S)} \end{array} \right]$$

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

$$\text{where } v_{\text{mapp}} = \frac{k_2 \cdot E_0}{1 + \frac{I}{K_I}} = \frac{v_m}{1 + \frac{I}{K_I}} \quad \leftarrow \text{As } I \uparrow, v_{\text{mapp}} \downarrow.$$

$$K_{\text{mapp}} = \frac{K_m}{1 + \frac{I}{K_I}} \quad \leftarrow \text{As } I \uparrow, K_{\text{mapp}} \downarrow.$$

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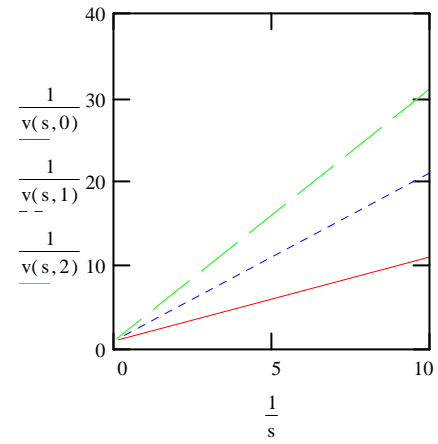
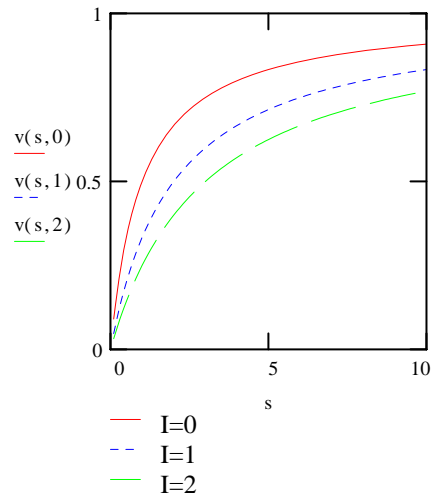
**Velocity and Lineweaver-Burk Plots**


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**1. Competitive Inhibition.**

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

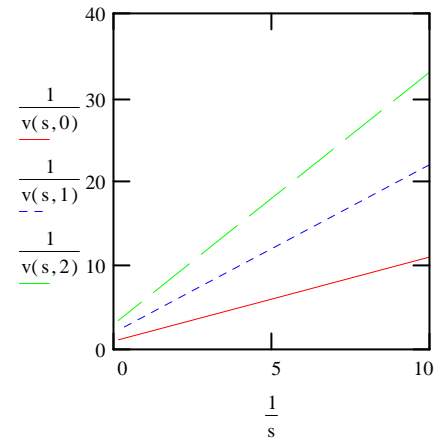
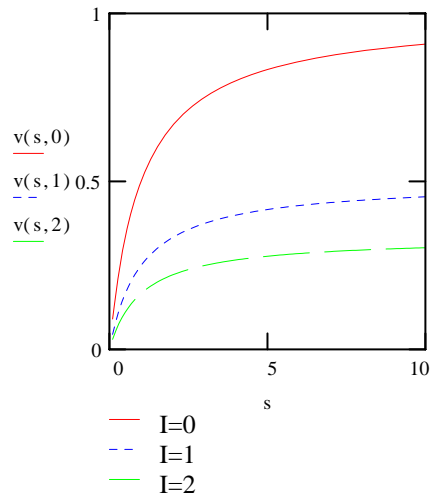
$s := 0.1, 0.2 \dots 10$



Common intercept; increased slope.

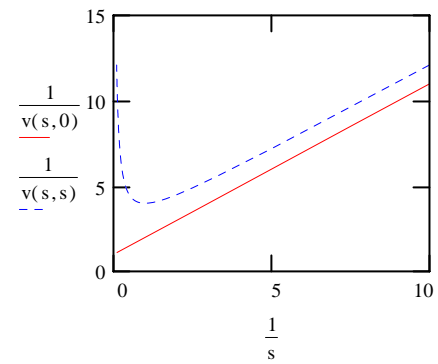
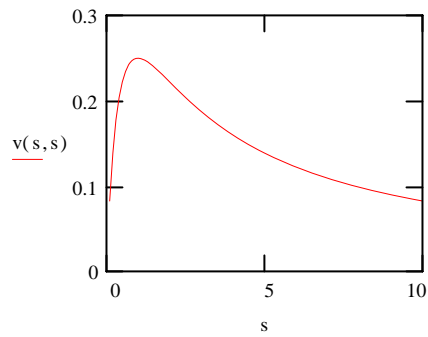
## 2. Non-competitive Inhibition.

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



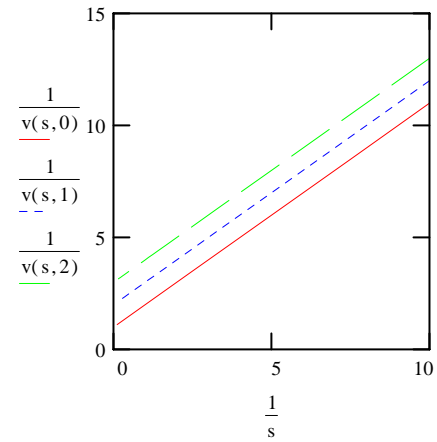
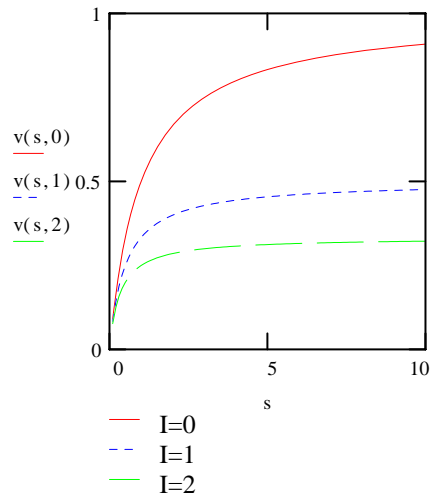
Increased intercept & slope.

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



### 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,  $I=S$

