Models for the kinetics of enzymes with product inhibition

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Outline

- Introduction

- Enzymes with competitive inhibition by product
  - Kinetics
  - Mathematical model

- Enzymes with non-competitive inhibition by product
  - Kinetics
  - Mathematical model
Enzymes

- known over a century
- nature’s sustainable catalysts,
- bio-compatible,
- biodegradable,
- from renewable resources.
Introduction

Enzymes

- known over a century
- nature’s sustainable catalysts,
- bio-compatible,
- biodegradable,
- from renewable resources.
- proteins responsible for thousands of metabolic processes.
- molecular weights: 10,000 to 2,000,000 Dalton
- able to reduce the activation energy of reactions.
Figure: Activation energy. From [2].
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- competitive inhibition: the substrate and inhibitor cannot bind to the enzyme at the same time.
- uncompetitive inhibition: the inhibitor binds only to the enzyme-substrate complex.
- non-competitive inhibition: the binding of the inhibitor to the enzyme reduces its activity but does not affect the binding of substrate.
- mixed inhibition: the inhibitor can bind to the enzyme at the same time as the substrate.
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Competitive inhibition by product

**Figure:** Enzyme $E$.

**Figure:** Substrate $S$.

**Figure:** Product $P$.

**Figure:** $ES$ complex.

**Figure:** $EP$ complex.

Kinetic equations:

$$S + E \rightleftharpoons k_1 ES \rightarrow E + P,$$

$$P + E \rightleftharpoons k_2 EP.$$
Competitive inhibition by product

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Kinetic equations:

$$S + E \xrightarrow{k_1} k_{-1} ES \xrightarrow{k_0} E + P,$$

$$P + E \xrightarrow{k_2} k_{-2} EP,$$
Competitive inhibition by product

Mathematical model:

\[
\begin{align*}
\frac{d[E]}{dt} &= (k_0 + k_{-1})[ES] + k_{-2}[EP] - k_1[E][S] - k_2[E][P], \\
\frac{d[ES]}{dt} &= k_1[E][S] - (k_0 + k_{-1})[ES], \\
\frac{d[EP]}{dt} &= k_2[E][P] - k_{-2}[EP], \\
\frac{d[S]}{dt} &= k_{-1}[ES] + k_1[E][S], \\
\frac{d[P]}{dt} &= k_0[ES] + k_{-2}[EP] - k_2[E][P],
\end{align*}
\]

where \([A]\) is the concentration of compound \(A\).
Competitive inhibition by product

Dimensionless variables:

\[ e = \frac{[E]}{e_0}, \quad c_1 = \frac{[ES]}{e_0}, \quad c_2 = \frac{[EP]}{e_0}, \quad s = \frac{[S]}{s_0}, \quad p = \frac{[P]}{s_0}, \quad \tau = e_0 k_1 t. \]
Competitive inhibition by product

\[
\begin{align*}
\epsilon \frac{dc_1}{d\tau} &= -(s + \hat{k}_0 + \hat{k}_{-1})c_1 - sc_2 + s, \\
\epsilon \frac{dc_2}{d\tau} &= \hat{k}_2 \left(-pc_1 - \left(p + \frac{\hat{k}_{-2}}{\hat{k}_2}\right)c_2 + p\right), \\
\frac{ds}{d\tau} &= \hat{k}_{-1}c_1 - s(1 - c_1 - c_2), \\
\frac{dp}{d\tau} &= \hat{k}_0c_1 + \hat{k}_{-2}c_2 - \hat{k}_2p(1 - c_1 - c_2),
\end{align*}
\]

where

\[
\epsilon = \frac{e_0}{s_0}, \quad \hat{k}_0 = \frac{k_0}{k_1s_0}, \quad \hat{k}_{-1} = \frac{k_{-1}}{k_1s_0}, \quad \hat{k}_2 = \frac{k_2}{k_1}, \quad \hat{k}_{-2} = \frac{k_{-2}}{k_1s_0}.
\]
Product formation rate:

\[ v = \frac{d[P]}{dt} = \frac{V_{\text{max}}[S]}{[S] + K_m \left(1 + \frac{[P]}{K_D}\right)}, \]

where

- \( V_{\text{max}} = k_0 e_0 \) : maximal rate for enzyme,
- \( K_m \) : Michaelis-Menten constant for enzyme,
- \( K_D \) : dissociation constant for product.
Figure: Effect of product concentration on the Michaelis-Menten constant for enzyme.
Non-competitive inhibition by product

Figure: Enzyme $E$.

Figure: Substrate $S$.

Figure: Product $P$.

Figure: $ES$ complex.

Figure: $EP$ complex.

Figure: $ESP$ complex.

$S + E \overset{k_1}{\rightleftharpoons} [S][E] \overset{k_{-1}}{\rightarrow} E + P,$

$P + E \overset{k_2}{\rightleftharpoons} [P][E] \overset{k_{-2}}{\rightarrow} E + S.$
Non-competitive inhibition by product

**Figure:** Enzyme $E$.

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\[
S + E \xrightleftharpoons[k_1]{k_0} ES \rightarrow E + P,
\]

\[
P + E \xrightleftharpoons[k_2]{k_{-2}} EP,
\]

\[
S + EP \xrightleftharpoons[k_1]{k_{-1}} ESP,
\]

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Product inhibition

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Non-competitive inhibition by product

Product formation rate

\[ v = \frac{d[P]}{dt} = \frac{V_{\text{max}} [S]^2 + A[S]}{1 + [P]/K_{D,P} [S]^2 + B[S] + C}, \]

where

\[ A = K_{D,S} + (1 + [P]/K_{D,P})k_{-2}/k_1, \]
\[ B = K_{D,S} + K_m + (1 + [P]/K_{D,P})k_{-2}/k_1, \]
\[ C = K_{D,S}[K_m + (1 + [P]/K_{D,P})k_{-2}/k_1] + k_0 k_{-2}/k_1^2, \]
\[ K_{D,S} = \frac{k_{-1}}{k_1}, \quad K_{D,P} = \frac{k_{-2}}{k_2}, \quad K_m = \frac{k_0 + k_{-1}}{k_1}. \]
Non-competitive inhibition by product

Figure: Effect of product concentration on $V_{\text{max}}$. 
THANK YOU FOR YOUR ATTENTION!

Questions or Comments?!?! ;}