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
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  - Mathematical model

Introduction

Enzymes

- known over a century
- nature's sustainable catalysts,
- bio-compatible,
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- nature's sustainable catalysts,
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- 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.

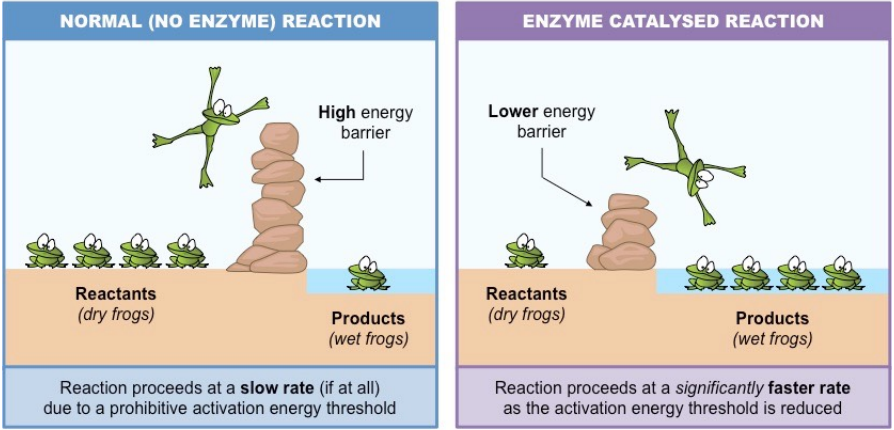

Figure: Activation energy. From [2].

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- 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.

Competitive inhibition by product

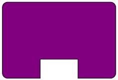


Figure: Enzyme *E*.

Figure: Product *P*.

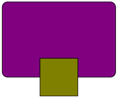
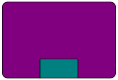


Figure: *EP* complex.

Figure: Substrate *S*.



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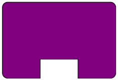

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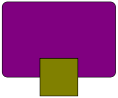

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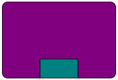


Figure: ES complex.

Kinetic equations:

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

$$P + E \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} EP,$$

Competitive inhibition by product

Mathematical model:

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

where $[A]$ is the concentration of compound A.

Competitive inhibition by product

Dimensionless variables:

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

Competitive inhibition by product

$$
\begin{aligned}
\epsilon \frac{dc_1}{d\tau} &= -(s + \hat{k}_0 + \hat{k}_{-1})c_1 - sc_2 + s, & (1)\\
\epsilon \frac{dc_2}{d\tau} &= \hat{k}_2 \left(-pc_1 - (p + \hat{k}_{-2}/\hat{k}_2)c_2 + p \right), & (2)\\
\frac{ds}{d\tau} &= \hat{k}_{-1}c_1 - s(1 - c_1 - c_2)), & (3)\\
\frac{dp}{d\tau} &= \hat{k}_0 c_1 + \hat{k}_{-2}c_2 - \hat{k}_2 p(1 - c_1 - c_2), & (4)
\end{aligned}
$$

where

$$
\epsilon = \frac{e_0}{s_0}, \hat{k}_0 = \frac{k_0}{k_1 s_0}, \hat{k}_{-1} = \frac{k_{-1}}{k_1 s_0}, \hat{k}_2 = \frac{k_2}{k_1}, \hat{k}_{-2} = \frac{k_{-2}}{k_1 s_0}.
$$

Competitive inhibition by product

Product formation rate:

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

where

- $V_{max} = k_0 e_0$: maximal rate for enzyme,
- K_m: Michaelis-Menten constant for enzyme,
- K_D : dissociation constant for product.

Competitive inhibition by product

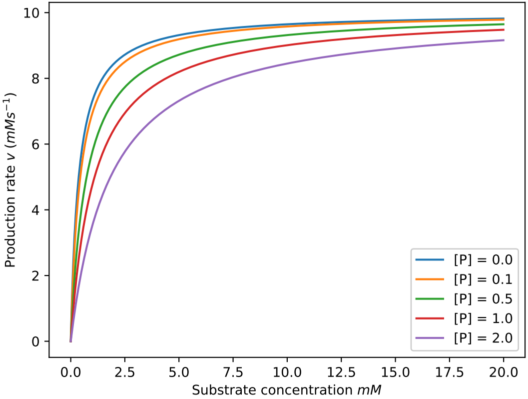


Figure: Effect of product concentration on the Michaelis-Menten constant for enzyme.

Non-competitive inhibition by product

Figure: Enzyme E.

Figure: Product P.

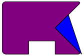
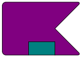


Figure: EP complex.

Figure: Substrate S.



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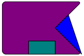

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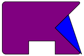

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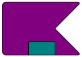

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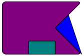

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Non-competitive inhibition by product

Product formation rate

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

where

$$\begin{aligned} A &= K_{D,S} + (1 + [P]/K_{D,P})k_{-2}/k_1, \\ B &= K_{D,S} + K_m + (1 + [P]/K_{D,P})k_{-2}/k_1, \\ C &= K_{D,S}[K_m + (1 + [P]/K_{D,P})k_{-2}/k_1] + k_0 k_{-2}/k_1^2, \end{aligned}$$

$$K_{D,S} = \frac{k_{-1}}{k_1}, \qquad K_{D,P} = \frac{k_{-2}}{k_2}, \qquad K_m = \frac{k_0 + k_{-1}}{k_1}.$$

Non-competitive inhibition by product

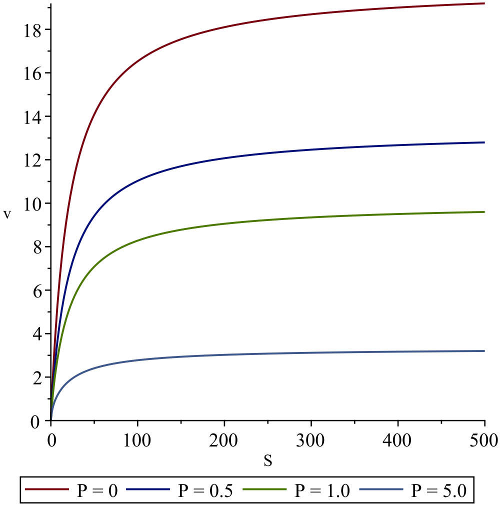

Figure: Effect of product concentration on V_{max}.

THANK YOU FOR YOUR ATTENTION!

Questions or Comments?!?! ;)

[1] http://shodhganga.inflibnet.ac.in/bitstream/10603/100595/7/07_chapter%201.pdf. Last accessed: 07/03/2019.
[2] http://ib.bioninja.com.au/higher-level/topic-8-metabolism-cell/untitled-6/activation-energy.html. Last accessed: 07/03/2019.
[3] Mark H. Holmes, *Introduction to the Foundations of Applied Mathematics*. Springer Science+Business Media, LLC 2009.