BIOMENG 261

TISSUE AND BIOMOLECULAR ENGINEERING

Module I: Reaction kinetics and systems biology

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MODULE OVERVIEW

Reaction kinetics and systems biology (*Oliver Maclaren*)

[11 lectures/3 tutorials/2 labs]

1. *Basic principles: modelling with reaction kinetics* [4 lectures]

   Conservation, directional and constitutive principles. Mass action. Enzyme kinetics. Enzyme regulation. Mathematical/graphical tools for analysis and fitting.

2. *Systems biology I: signalling and metabolic systems* [2 lectures]

   Overview of systems biology. Modelling signalling systems using reaction kinetics. Introduction to parameter estimation. Modelling metabolic systems using reaction kinetics. Flux balance analysis and constraint-based methods.

3. *Systems biology II: genetic systems* [3 lectures]

   Modelling genes and gene regulation using reaction kinetics. Gene regulatory networks, transcriptomics and analysis of microarray data.

LECTURE 2 ENZYME KINETICS

- Enzymes
- The Michaelis-Menten model
- Quasi-equilibrium and quasi-steady-state analysis
- Fitting to data

ENZYMES: MOTIVATION/IDEA

$$A + B \longrightarrow C$$

might be

- *Possible* (thermodynamically favourable)

but still

- *Too slow* (kinetic 'path' takes too long)

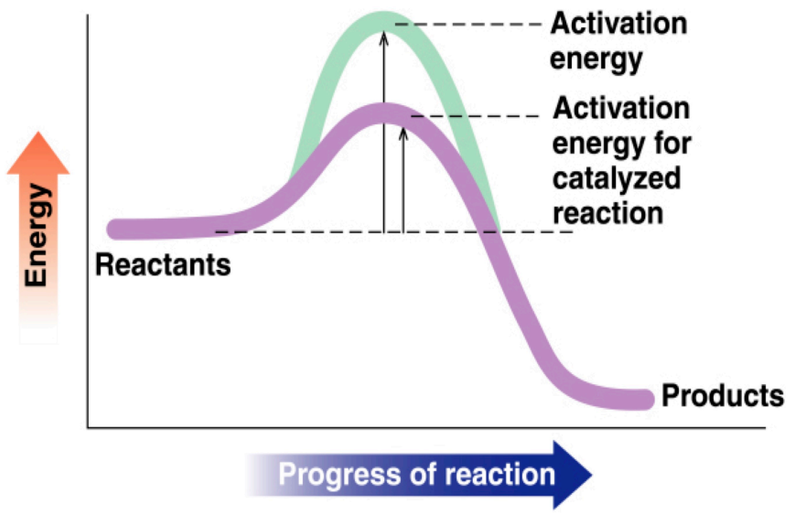
Q: Can we speed it up, without changing the start and end points?

CATALYSTS

A *catalyst* is a substance that

- Can speed up a reaction ('help along the reaction path')
- Doesn't change the start and end points (overall free energy is the same)
- Are not used up in the reaction themselves

CATALYSTS


Activation energy
Activation energy for catalyzed reaction
Energy
Reactants
Products
Progress of reaction

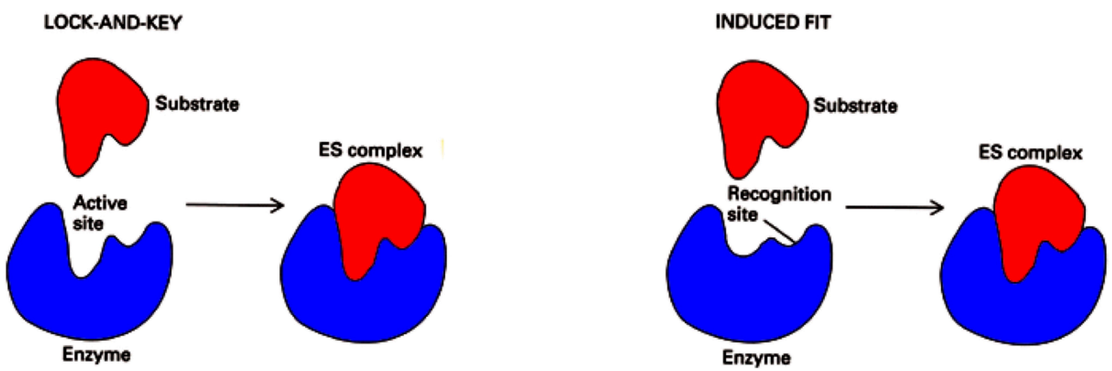
ENZYMES

An enzyme is a biological catalyst

- Usually proteins/large macromolecules
- Think: 'helper machines'
- Usually end in '-ase'
  - perme*ase*
  - kin*ase*
  - etc*ase*

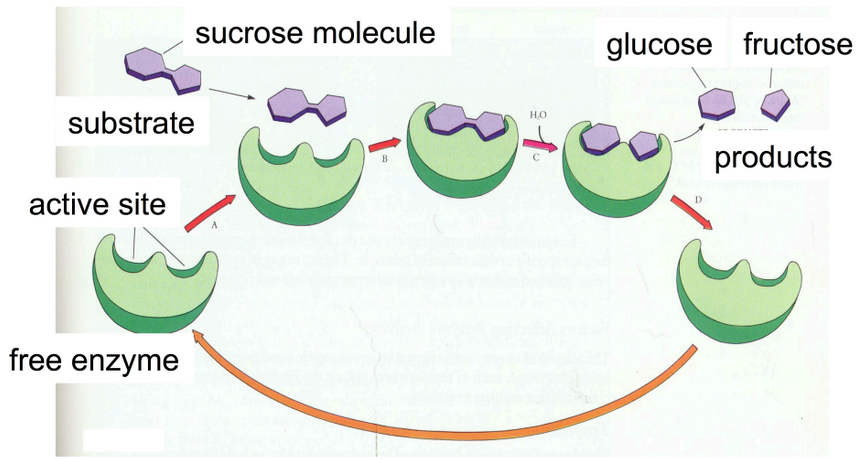
ENZYMES: MECHANISM(S)

- 'Lock and key': rigid enzyme
- 'Induced fit': same basic idea but deformable enzyme

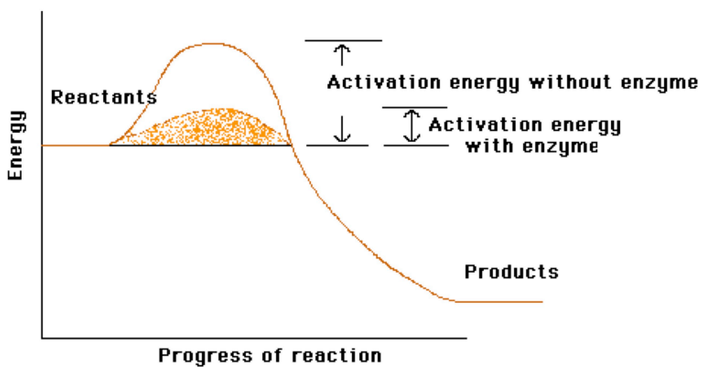


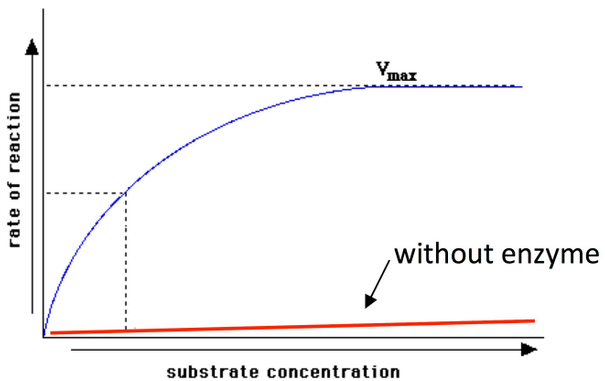
ENZYMES: EXAMPLE

Hydrolysis ('splitting') of sucrose into glucose and fructose



ENZYMES: EFFECT





Problem: *nonlinear* in 'substrate' (reactants)

But mass action would be rate = $k[S]$, i.e. linear!

THE MICHAELIS-MENTEN MODEL

Michaelis-Menten (1913) introduced one of the first, and simplest, mathematical models of enzyme activity

Each step of full system obeys mass action

But result is

The overall, effective $S \longrightarrow P$ reaction does not obey mass action

THE MICHAELIS-MENTEN MODEL: DERVIATION

Assumed reaction mechanism:

$$\mathrm{S+E} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{C} \xrightarrow{k_2} \mathrm{P+E}$$

THE MICHAELIS-MENTEN MODEL: FULL MODEL

Full system of equations:

$$\frac{\mathrm{d}[\mathrm{S}]}{\mathrm{d}t} = -k_1[\mathrm{E}][\mathrm{S}] + k_{-1}[\mathrm{C}]$$

$$\frac{\mathrm{d}[\mathrm{E}]}{\mathrm{d}t} = -k_1[\mathrm{E}][\mathrm{S}] + (k_{-1} + k_2)[\mathrm{C}]$$

$$\frac{\mathrm{d}[\mathrm{C}]}{\mathrm{d}t} = k_1[\mathrm{E}][\mathrm{S}] - (k_{-1} + k_2)[\mathrm{C}]$$

$$\frac{\mathrm{d}[\mathrm{P}]}{\mathrm{d}t} = k_2[\mathrm{C}]$$

Initial conditions:

$$[\mathrm{S}](0) = \mathrm{S}_0, \quad [\mathrm{E}](0) = \mathrm{E}_0, \quad [\mathrm{C}](0) = 0, \quad [\mathrm{P}](0) = 0$$

THE MICHAELIS-MENTEN MODEL: REDUCED MODEL

Goal: reduction to 'effective' constitutive equation for

$$S \longrightarrow P$$

i.e.

$$J_P = \frac{d[P]}{dt} = f([S])$$

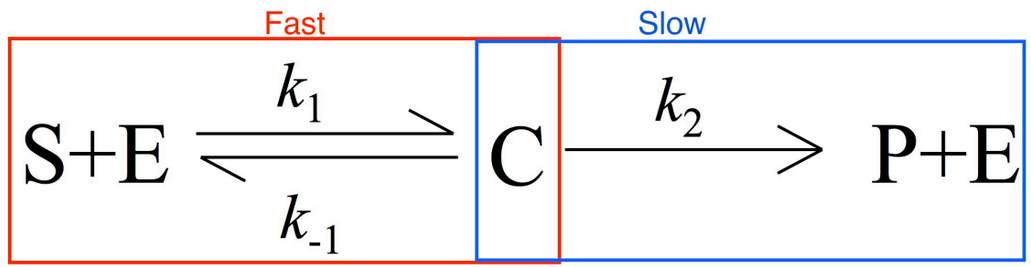
Note: people often use v instead of J in this context.

ANALYSIS METHODS

Recall: quasi-equilibrium vs quasi-steady-state

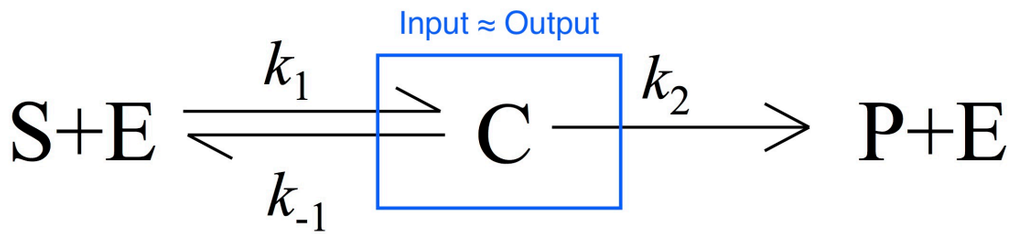
- *Equilibrium*: forward and backward components of a *single reaction balanced*
- *Steady state*: *concentrations constant* in time
  - multiple reactions into a particular compartment balance each other; may be unbalanced elsewhere

QUASI-EQUILIBRIUM ANALYSIS



- Assume fast reaction quickly reaches equilibrium.

QUASI-STEADY-STATE ANALYSIS



- Assume 'inputs and outputs' to $[C]$ quickly reach balance.

UPSHOT: THE MICHAELIS-MENTEN CONSTITUTIVE EQUATION

Both result in the same *form*:

$$v([S]) := J_P([S]) = \frac{d[P]}{dt} = \frac{V_{max}[S]}{K_M + [S]}$$

with different K_M in terms of elementary steps - often just treat *empirically*, i.e. fit K_M. Notes:

- A *nonlinear* constitutive equation for what would usually be a linear mass action reaction.

NOTE: LARGE VS SMALL?

- Always compare quantities with the *same units*
- *Ratio* is then independent of units i.e. *dimensionless*

e.g. quasi-equilibrium compare:

$$\frac{k_2}{k_{-1}} \ll 1?$$

quasi-steady state compare:

$$\frac{E_0}{S_0} \ll 1?$$

Justification.

USE FOR FITTING DATA: LINEWEAVER-BURK PLOTS

To fit to data we can *rewrite* the Michaelis-Menten relation

$$v = \frac{V_{\max}[S]}{K_M + [S]}$$

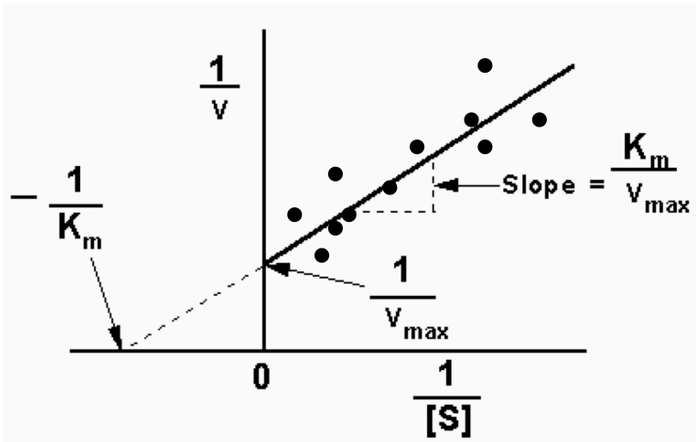
as

$$\frac{1}{v} = \frac{K_M}{V_{max}}\frac{1}{[S]} + \frac{1}{V_{max}}$$

i.e. $y = mx + c$ for $y = \frac{1}{v}$ and $x = \frac{1}{[S]}$.

USE FOR FITTING DATA: LINEWEAVER-BURK PLOTS

Called a Lineweaver-Burk plot.



Can also just fit original equation for a range of initial conditions.