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 3 ENZYME REGULATION: INHIBITION AND ACTIVATION

- Types of enzyme regulation
- Example: competitive inhibition
- Comments on quasi-steady-state analysis

ENZYMES REGULATION: MOTIVATION/IDEA

Enzyme catalysed reactions are controlled/regulated in various ways

E.g.

- *Amount* (how many enzymes)
  - E.g. via gene expression (see later)
- *Activity* ('on' and 'off', 'up' and 'down')
  - E.g. via regulatory molecules binding to enzyme

REGULATION OF ENZYMES ACTIVITY

Regulatory molecules that bind to enzyme:

- *Activator*: 'turn up' enzyme
- *Inhibitor*: 'turn down' enzyme

IRREVERSIBLE VS REVERSIBLE REGULATION

Irreversible:

- E.g. toxin that 'shuts down' enzyme permanently
- Not so good for control!
- Typically via strong (covalent) interaction

Reversible:

- *Better for control!*
- Typically via weaker (non-covalent) interaction

We'll (mainly) focus on reversible regulation and 'control'

REVERSIBLE REGULATION TYPES

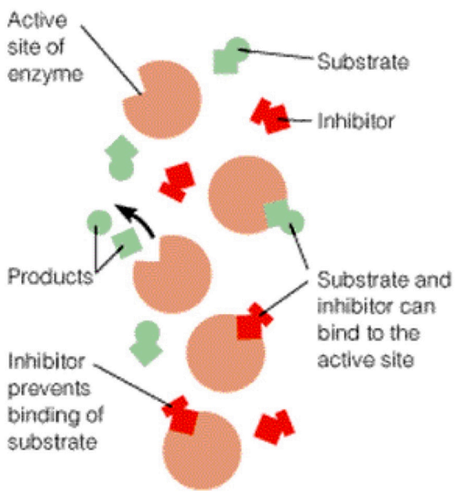
Behaviour/effect type:

- Competitive
- Noncompetitive
- Uncompetitive

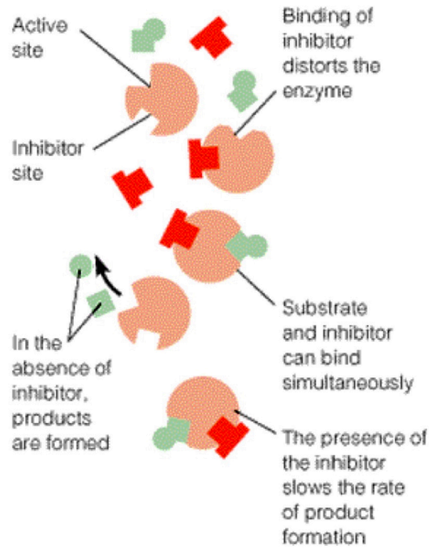
Location of regulation interaction:

- active site (where substrate binds)
- allosteric site (not where substrate binds)

LOCATION OF REGULATION INTERACTION



direct



allosteric

BEHAVIOUR/EFFECT INHIBITOR TYPE

Competitive:

- Substrate and inhibitor can't be bound at the same time

Uncompetitive:

- Inhibitor can only bind to substrate-enzyme complex (not free enzyme)
- Prevents both product step and reversible unbinding step

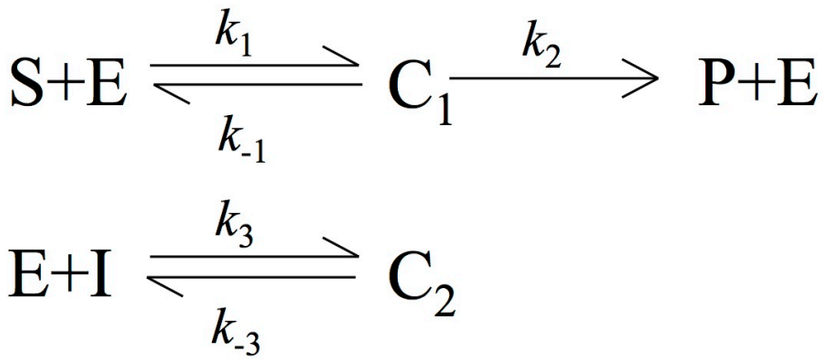
Noncompetitive:

- Inhibitor can bind to either/both enzyme and complex
- Only slows product step
- Doesn't affect binding of substrate

MODEL

Goal here: derive model of direct, competitive inhibition

MODEL SCHEME



MODEL SUMMARY

$$\frac{d[S]}{dt} = -k_1[E][S] + k_{-1}[C_1]$$

$$\frac{d[I]}{dt} = -k_3[E][I] + k_{-3}[C_2]$$

$$\frac{d[C_1]}{dt} = k_1[E][S] - (k_{-1} + k_2)[C_1]$$

$$\frac{d[C_2]}{dt} = k_3[E][I] - k_{-3}[C_2]$$

and the reaction rate

$$v = \frac{d[P]}{dt} = k_2[C_1]$$

- Enzyme is conserved

$$[E]+[C_1]+[C_2]=E_0$$

REDUCTION: 'REMOVING' THE ENZYME

Goal is to *eliminate the enzyme terms* from the equations using:

- Conservation of total enzyme (including its complex form)
- Quasi-steady-state for C_1 and C_2

Result: as before we get an effective, MM-style constitutive equation for

$$S \longrightarrow P$$

but now the constants depend on I!

UPSHOT

Get *same MM form* of equation, but *modified* K_M constant:

$$J_P = v = \frac{V_{\text{max}}[S]}{K_M^{\text{new}} + [S]}$$

where here

$$K_M^{\text{new}} = K_M^{\text{old}}(1 + \frac{[I]}{K_I})$$

and

$$K_I = \frac{k_{-3}}{k_3}$$

NOTE ON THE 'QUASI' IN QSS

See handout.