

# **BIOMENG 261**

## **TISSUE AND BIOMOLECULAR ENGINEERING**

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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



might be

- *Possible* (thermodynamically favourable)  
but still
- *Too slow* (kinetic 'path' takes too long)

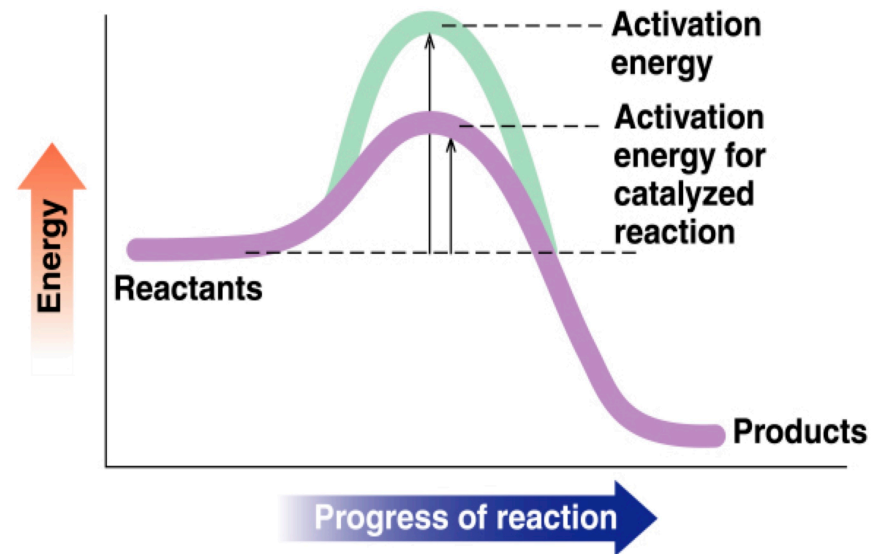
*Q: Can we speed it up, without changing  
the start and end points?*

# 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



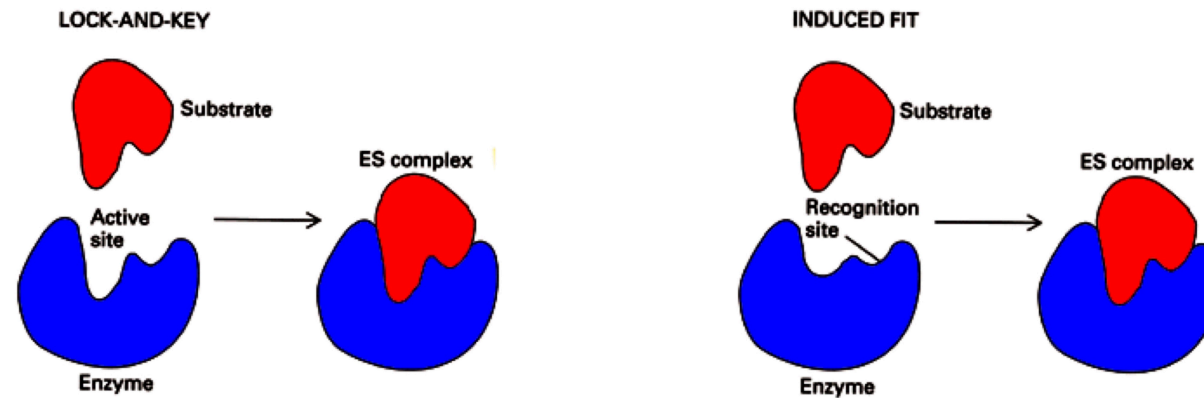
# ENZYMES

*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)

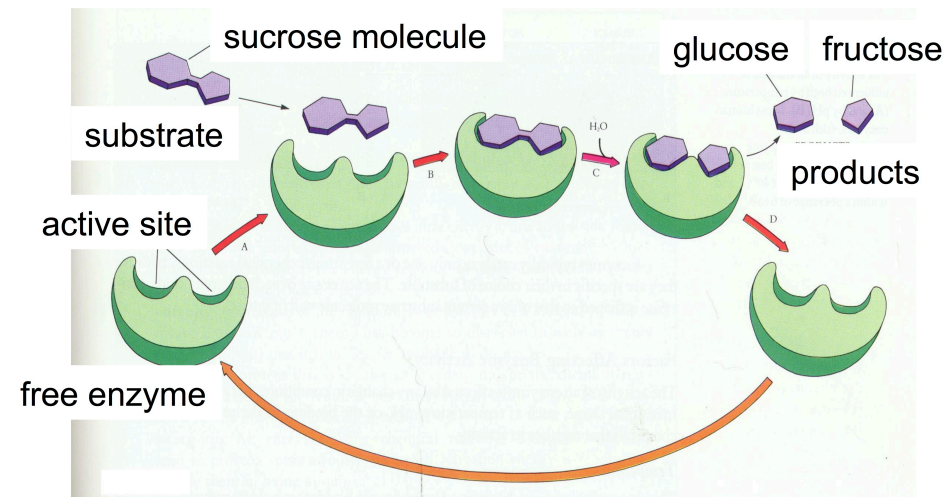
- 'Lock and key': rigid enzyme
- 'Induced fit': same basic idea but deformable enzyme



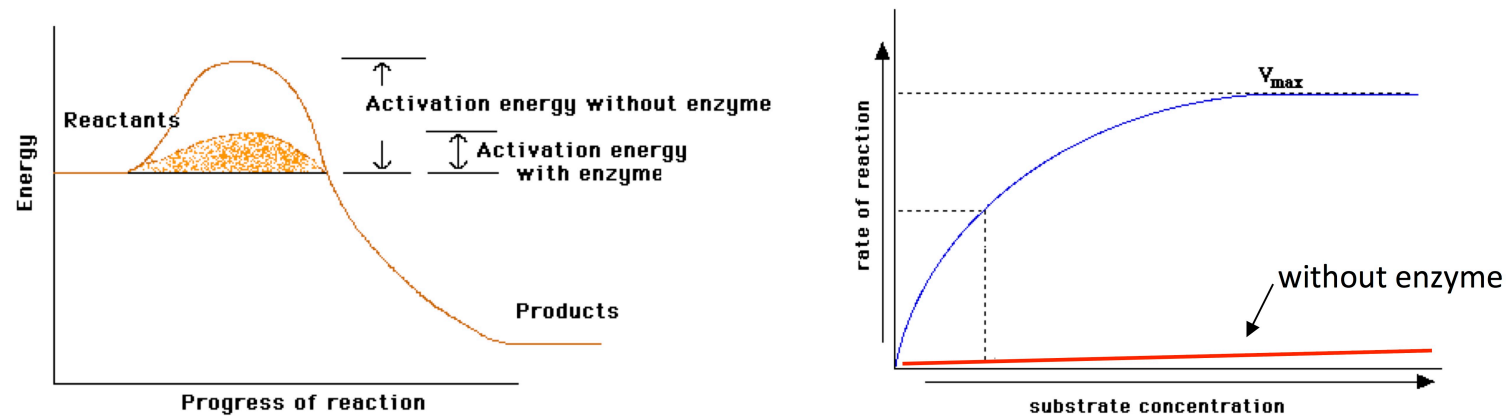


# ENZYMES: EXAMPLE

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

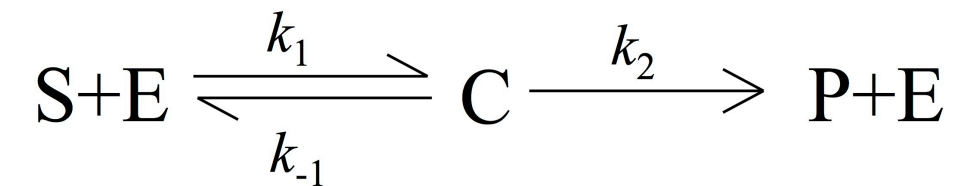
*Each step of **full system** obeys mass action*

But result is

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

# THE MICHAELIS-MENTEN MODEL: DERVIATION

Assumed reaction mechanism:



# THE MICHAELIS-MENTEN MODEL: FULL MODEL

Full system of equations:

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

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

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

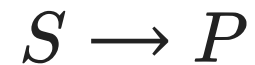
$$\frac{d[P]}{dt} = k_2[C]$$

Initial conditions:

$$[S](0) = S_0, \quad [E](0) = E_0, \quad [C](0) = 0, \quad [P](0) = 0$$

# THE MICHAELIS-MENTEN MODEL: REDUCED MODEL

Goal: reduction to 'effective' constitutive equation for



i.e.

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

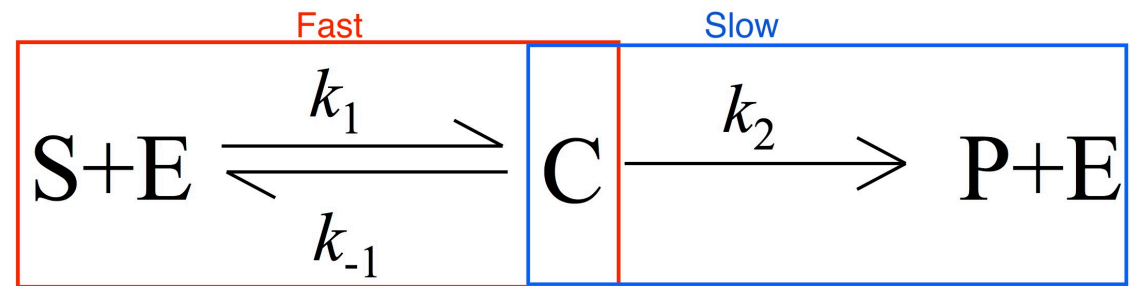
Note: people often use  $v$  instead of  $J$  in this context.

# 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

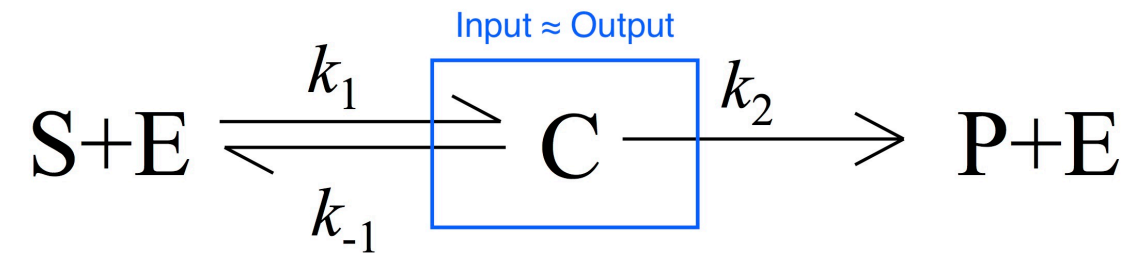
# QUASI-EQUILIBRIUM ANALYSIS



- 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

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

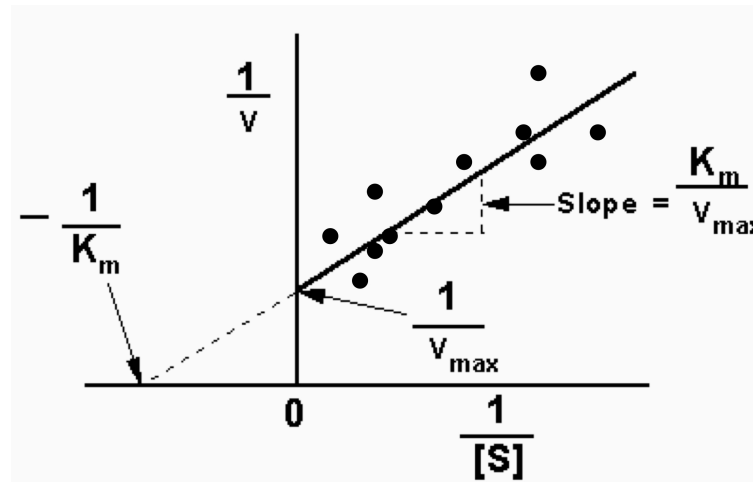
as

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

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.