

BIOMENG 261

TISSUE AND BIOMOLECULAR ENGINEERING

Module I: Reaction kinetics and systems biology

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COURSE

- Reaction kinetics and systems of reactions (weeks 1-4)
- Biological engineering laboratory techniques (weeks 5-10)
- Ethics in biomedical engineering practice and research (weeks 11-12)

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MODULE OVERVIEW

Reaction kinetics and systems biology (*Oliver Maclarens*)

[12 lectures/3 tutorials/2 labs]

1. Basic principles: modelling with reaction kinetics [6 lectures]

Physical principles: conservation, directional and constitutive. Reaction modelling. Mass action. Enzyme kinetics. Enzyme regulation. Mathematical/graphical tools for analysis and fitting.

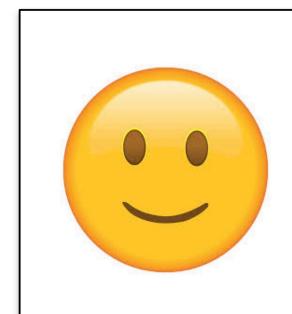
2. Systems biology I: overview, signalling and metabolic systems [3 lectures]

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.

PEOPLE



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ASSESSMENT

Coursework: 60%, Exam: 40%

- Module 1 Coursework:

- Computer labs/assignments (2 x 2.5%) - Weeks 2 & 3
- Test (10%) - Week 5

- Module 2 Coursework:

- Lab assessments (6 labs, 30%)
- Test (10%)

- Module 3 Coursework:

- Assignment (5%)

REFERENCES

No course book...but see Canvas handout for recommended resources.

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SCHEDULE

Module 1 (4 weeks)

- Lectures: Monday (1-2pm), Tuesday (3-4pm), Wednesday (2-3pm)
- Tutorials: Thursday (1-2pm) - weeks 2, 3, 4. Optional; do sheets in own time, can ask questions, discuss in tutorial.
- Labs: Friday (10am-1pm) - weeks 2 and 3 only. Will form basis of computer assignments.

MOTIVATION

...understanding, simulating, analysing, creating...biological systems using mathematics, computation and experimentation

Biology is hard! (Arguably) more difficult than traditional engineering, physics etc.

Why? *Complexity!* Molecules, Genes, Proteins, Cells, Tissues, Organs, Organisms...

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MOTIVATION

How do we integrate all this and understand such complex systems?

Modelling, simulation, data analysis, experiments...etc.

Trade-offs are key: prediction vs understanding, fit vs complexity, reduction vs emergence, theory vs experiment etc

Also: need *basic physical principles* and *mathematical language(s)*

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BASIC PHYSICAL PRINCIPLES FOR UNDERSTANDING BIOLOGICAL SYSTEMS

Conservation: energy, *mass*, momentum

Directional: entropy increases, *free energy decreases*

Constitutive: the 'law' of *mass action* (reaction rates proportional to chances of collisions)

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LECTURE 1 BASIC PRINCIPLES OF REACTION MODELLING

- Physical principles: conservation, directional, constitutive
- Reactions and their graphical representations
- Units and dimensions
- Reversible/irreversible reactions

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BASIC PHYSICAL PRINCIPLES FOR UNDERSTANDING BIOLOGICAL SYSTEMS

Conservation: *possible*

Directional: *probable*

Constitutive: *actual*

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REACTIONS

A surprising number of biological phenomena can be considered as *built up from simple reactions of the form*

Reactants → Products

i.e.



This module will largely focus on *setting up, modelling, computing and analysing systems built up from such reactions using physical principles*

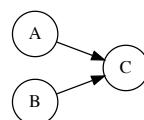
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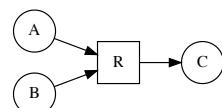
GRAPHICAL REPRESENTATIONS

Chemical/stoichiometric equation: $A + B \rightarrow C$

Reaction graph:



Petri-net-style representation:



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EXAMPLE

Steps

- Conservation of mass
- Constitutive equation ('law of mass action') for rate

LAW OF MASS ACTION

A 'law' in the way Newton's law of cooling, Hooke's law of elasticity, Ohm's law etc are 'laws' (i.e. not really!)

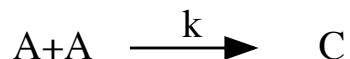
the rate of a chemical reaction is directly proportional to the product of all of the concentrations (or chemical activities in general) of the reactants

Can be motivated 'microscopically' or 'mechanistically' by collision theory.

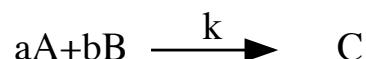
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MORE EXAMPLES

Example 1:



Example 2:



COMPLICATIONS

- Units and dimensions
- Reversible/irreversible reactions

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ORDER OF A REACTION

The **partial order** of a (mass-action-based) reaction for a given substance is the exponent (power) to which it is raised in the rate law.

The **overall order** of a (mass-action-based) reaction is the sum of the exponents of all the reactants in the rate law.

AMOUNTS VS CONCENTRATIONS

- **Amounts** (or numbers or masses etc) are conserved.
 - Dimensions: amount, number, etc
 - Units: moles, mol
- **Concentrations** are not, unless volume is constant.
- Dimensions: amount per volume
 - Units: Molar, M = mol/L

Example.

Q: What are the orders for the previous two examples?

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REVERSIBLE VS IRREVERSIBLE REACTIONS

Microscopically: all reactions are *reversible* (bidirectional)

Macroscopically: some more likely to occur than others
(effectively unidirectional)

Remember: *possible is not the same as probable*

Example, including determining equilibrium constants K_{eq}
for reactions

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EQUILIBRIUM VS STEADY STATE

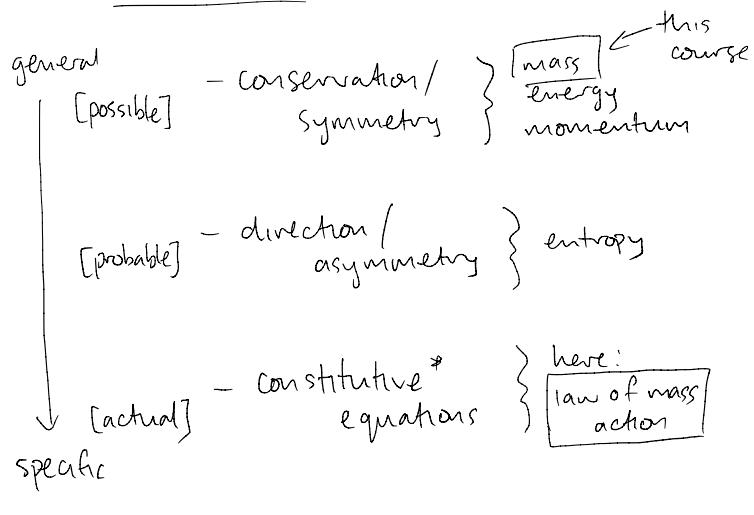
- *Equilibrium*: forward and backward components of a *single reaction balanced*
- *Steady state*: *concentrations constant* in time
 - multiple reactions into a particular compartment balance each other; may be unbalanced elsewhere

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Biomeng 261 Lecture 01: Basic Principles
of Reaction Modelling.

Idea : The behaviour of cells can
(partially) be understood / modelled
using chemical reaction modelling

Key Physical Principles

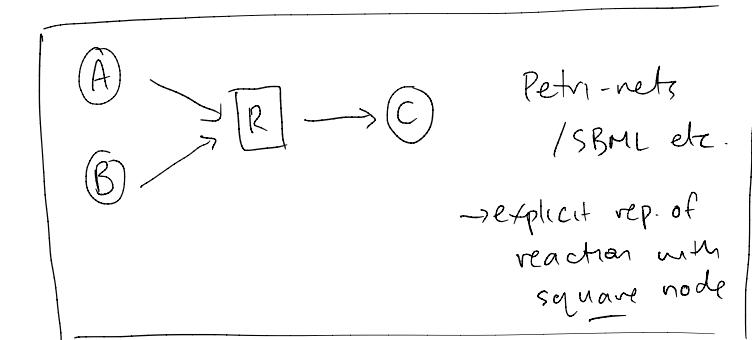
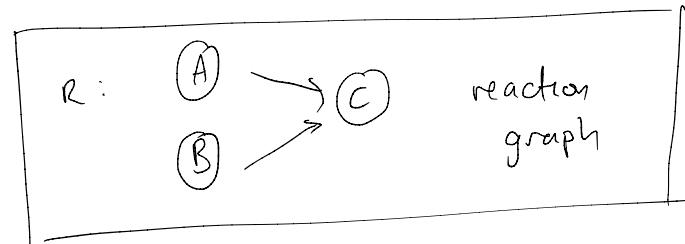
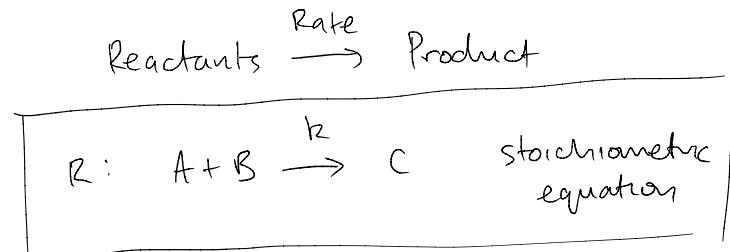


* like 'Hooke's law' $F = kx$
or 'Newton's gravitational law' $F = GMm/r^2$

→ think 'force' or 'flux'
modelling

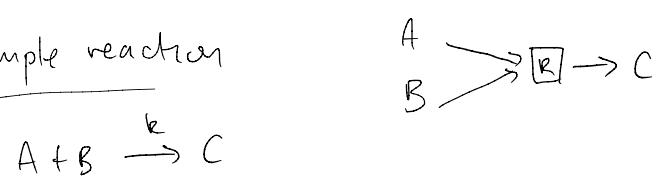
→ valid for some class of systems
but not all

Graphical representations



↳ helpful to treat reaction as 'object' of interest itself.

Example reaction



1. Conservation of mass

key: think in terms of the reaction itself:

each 'step' $\boxed{1A\downarrow, 1B\downarrow, 1C\uparrow}$

Flux \tilde{J} of reaction

$$\frac{dA}{dt} = -\tilde{J} \quad \left. \begin{array}{l} \\ \end{array} \right\} \text{note! Not eg } \tilde{J}/2$$

$$\frac{dB}{dt} = -\tilde{J}$$

$$\frac{dC}{dt} = +\tilde{J}$$

$\left[\begin{array}{l} \text{why } \tilde{J} \text{ & not } J? \\ \rightarrow \text{units; see later} \end{array} \right]$

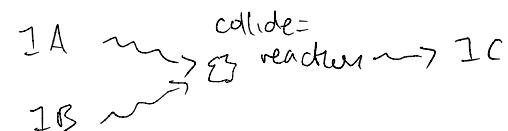
2. Specific model for flux \tilde{J}

'law' of mass action

- for 'elementary' reactions

- will assume more complex reactions are built up from simple.

Intuition: collision theory



rate \propto number of collisions

\propto number of A molecules

\propto number of B molecules

$= k \cdot A \cdot B \quad (\text{for } A+B \rightarrow C)$

$$\Rightarrow \boxed{\tilde{J} = k \cdot A \cdot B}$$

k : reaction rate 'constant'
[also depends on eg temperature
hotter = more collisions]

Finally

$$\begin{aligned}\frac{dA}{dt} &= -k \cdot A \cdot B \\ \frac{dB}{dt} &= -k \cdot A \cdot B \\ \frac{dC}{dt} &= +k \cdot A \cdot B\end{aligned}$$

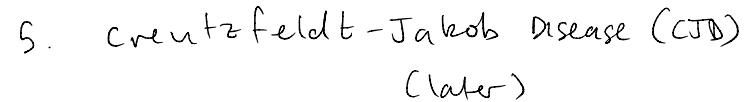
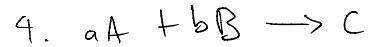
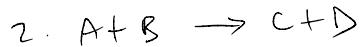
Mass action:

rate \propto number of collisions
of reactants

order of reaction:

number of reactants
colliding

Examples



each 'step': $\downarrow 2A, 1B$

conservation
(number
per
step) { $\begin{cases} \frac{d[A]}{dt} = -2J \\ \frac{d[B]}{dt} = +J \end{cases}$ } & $J = k[A]^2$ } chance
of
collisions

order = 2
 $\Rightarrow \left[\frac{d[A]}{dt} = -2k[A]^2 ; \frac{d[B]}{dt} = k[A]^2 \right]$

$$4. \frac{d[A]}{dt} = -aJ, \frac{d[B]}{dt} = -bJ$$

$$\frac{d[C]}{dt} = J, J = k[A]^a[B]^b$$

$$\underline{\text{order}} = a+b$$

^{re} partial order for A : a

partial order for B : b

overall order : a+b

Complications

- units & dimensions
- reversible / irreversible reactions

Amounts vs concentrations ?

Q: what is conserved ?

A: amount

$$\text{Amount} = (\text{Amount}/\text{Volume}) \times \text{Volume}$$

$$= [A] \times V$$

↑
concentration

if volume is constant

$$\frac{dA}{dt} = \frac{d(V[A])}{dt} = V \frac{d[A]}{dt} = \tilde{J}$$

$$\Rightarrow \frac{d[A]}{dt} = \frac{\tilde{J}}{V} = J$$

1 mol : Avogadro's number of molecules (6.022×10^{23})

1 Molar : 1 mol/litre : concentration
(M) typical uM-mM.

\tilde{J} : amount / time (eg mol/sec)

$$J : \frac{\tilde{J}}{V} = \frac{\text{amount}}{\text{time}} / \text{volume}$$

$$= \frac{\text{amount}}{\text{volume} \cdot \text{time}}$$

$$= \text{concentration} / \text{time}$$

(eg M/sec.)

Typically: $\frac{d[A]}{dt} = J$ } usually work with concentrations

But: Careful!

Leg if volume is changing.

Order & rate constant dimensions/units

1st order $J = k[A] = \frac{d[A]}{dt} \Rightarrow k = \frac{1}{\text{time}}$ (eg 1/sec.)

2nd order $J = k[A][B] = \frac{d[A]}{dt} \Rightarrow k = \frac{1}{\text{conc. time}}$ (eg M⁻¹s⁻¹)

→ we will look at dimensional analysis & scaling a bit later.

Reversible & irreversible reactions

Microscopic reversibility

[kinetics]

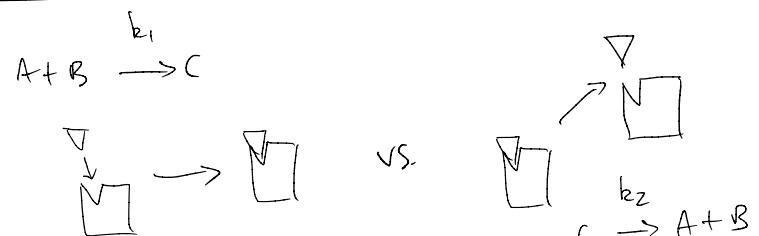
- all elementary reactions

can proceed in both directions

BUT: one direction might be more likely

Possible ≠ Probable

glass breaking
vs
glass spontaneously forming.

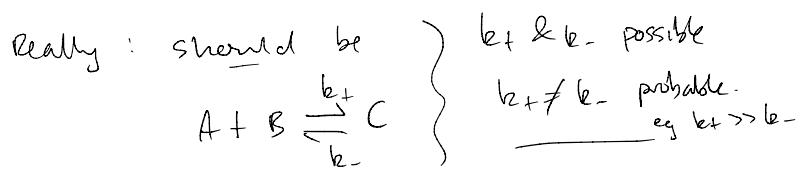


There are ways of encouraging one direction, so $k_1 \neq k_2$

Macroscopic irreversibility [thermo]

asymmetric { entropy increases / gibbs free energy decreases

Example



k_+ : forward reaction $A + B \rightarrow C$

k_- : reverse reaction $C \rightarrow A + B$

$$1. \frac{d[A]}{dt} = \frac{d[B]}{dt} = -J_+ + J_-$$

$$\frac{d[C]}{dt} = J_+ - J_-$$

$$2. J_+ = k_+[A][B]$$

$$J_- = k_-[C]$$

$$\Rightarrow \begin{cases} \frac{d[A]}{dt} = \frac{d[B]}{dt} = k_-[C] - k_+[A][B] \\ \frac{d[C]}{dt} = k_+[A][B] - k_-[C] \end{cases}$$

Assume $k_+ \neq k_-$

BUT: how do we measure/det

$k_+ > k_-$ or $k_+ < k_-$?

→ let reach equilibrium/steady state

- Equilibrium: reactions balanced
- Steady state: change in concentrations = 0

(Here: same, but not in general.)

set (eg want long time)

$$k_- [C]_{eq} - k_+ [A]_{eq} [B]_{eq} = 0$$

$$\Rightarrow K_{eq} := \frac{k_-}{k_+} = \frac{[A]_{eq} [B]_{eq}}{[C]_{eq}}$$

If K_{eq} { large: $[A]_{eq} [B]_{eq} \gg [C]_{eq}$
small: $[A]_{eq} [B]_{eq} \ll [C]_{eq}$

i.e { $\xleftarrow{k_-}$ reverse dominates
 $\xrightarrow{k_+}$ forward dominates

$\boxed{\text{If } k_+ \gg k_- \text{ we often approx as } A + B \xrightarrow{k} C}$ } "favors" * forward reaction

$\boxed{* K_{eq} \text{ & hence ratios of } k_-, k_+ \text{ etc}}$
can be related to Gibbs free energy & thermo.