

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)

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

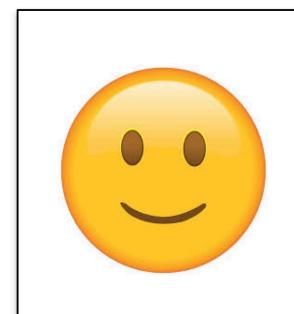
[3 lectures]

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.

SCHEDULE

Module 1 (4 weeks)

- Lectures: Monday (4-5pm), Tuesday (12-1pm), Wednesday (3-4pm)
- Tutorials: Thursday (11-12pm) - weeks 1, 2, 3, 4. Optional; do sheets in own time, can ask questions, discuss in tutorial.
- Computer 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...

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)*

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)

LECTURE 1 BASIC PRINCIPLES OF REACTION MODELLING

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

BASIC PHYSICAL PRINCIPLES FOR UNDERSTANDING BIOLOGICAL SYSTEMS

Conservation: *possible*

Directional: *probable*

Constitutive: *actual*

REACTIONS

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

Reactants \longrightarrow Products

i.e.



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

EXAMPLE

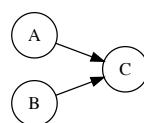
Steps

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

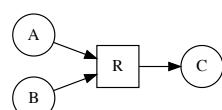
GRAPHICAL REPRESENTATIONS

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

Reaction graph:



Petri-net-style representation:



LAW OF MASS ACTION

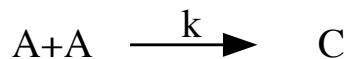
A 'law' in the way Newton's law of cooling, Hooke's law of elasticity, Ohm's law etc are 'laws' (i.e. not really!)

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

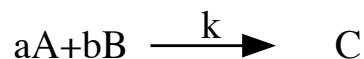
Can be motivated 'microscopically' or 'mechanistically' by collision theory.

MORE EXAMPLES

Example 1:



Example 2:



COMPLICATIONS

- Units and dimensions
- Reversible/irreversible reactions

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.

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

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.

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

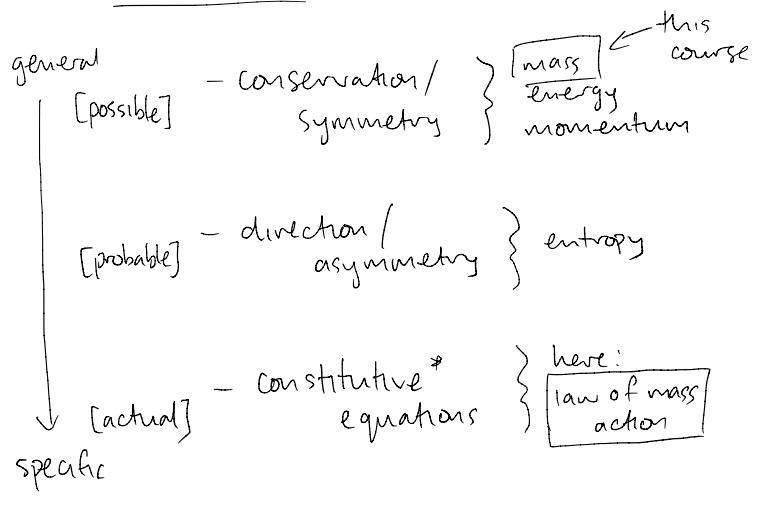
EQUILIBRIUM VS STEADY STATE

- *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

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

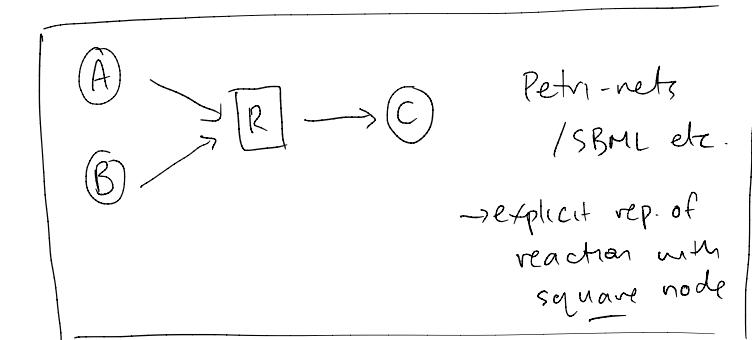
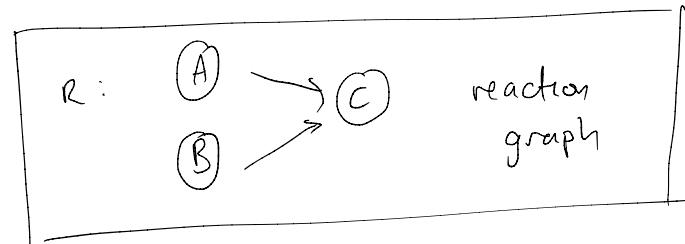
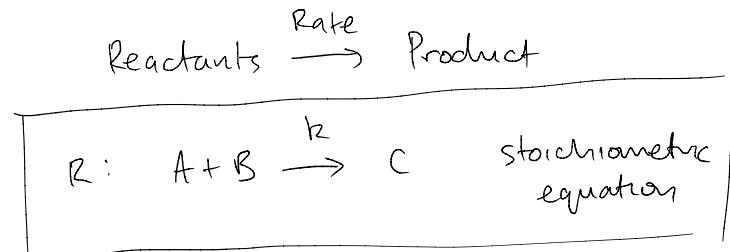


* like 'Hooke's law' $F = kx$
or 'Newton's gravitational law' $F = GMm/r^2$

→ think 'force' or 'flux'
modelling

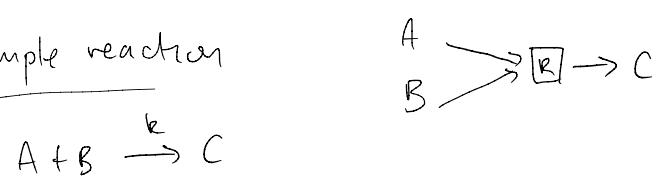
→ valid for some class of systems
but not all

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

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

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

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

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

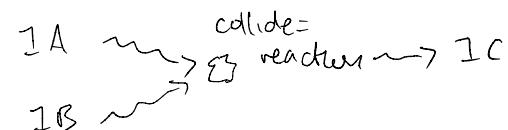
2. Specific model for flux \tilde{J}

'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

$= k \cdot A \cdot B$ (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

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

Examples

1. $A + A \rightarrow C$ ($2A \rightarrow B$)
2. $A + B \rightarrow C + D$
3. $A + B + C \rightarrow D$
4. $aA + bB \rightarrow C$
5. Creutzfeldt-Jakob Disease (CJD)
(later)

Mass action:

rate \propto number of collisions
of reactants

order of reaction:

number of reactants
colliding

1. R: $2A \rightarrow B$ } think in terms
of reactions

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

conservation
(number
per
step))

$$\left\{ \begin{array}{l} \frac{d[A]}{dt} = -2J \\ \frac{d[B]}{dt} = +J \end{array} \right\} \text{ & } J = k[A]^2 \quad \begin{array}{l} \text{chance} \\ \text{of} \\ \text{collisions} \end{array}$$

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]

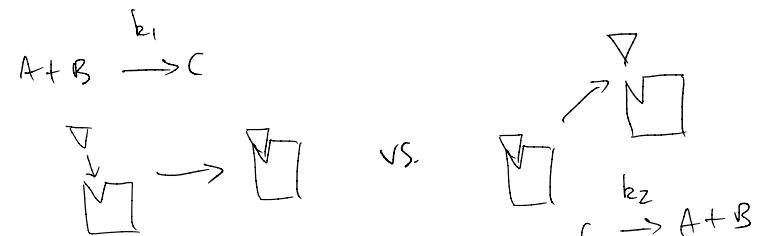
- all elementary reactions

can proceed in both directions

BUT: one direction might be more likely

Possible ≠ Probable

glass breaking
vs
glass spontaneously forming.

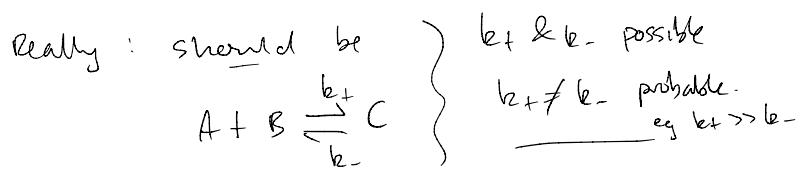


There are ways of encouraging one direction, so $k_1 \neq k_2$

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 (e.g. 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.