BIOMENG 261

TISSUE AND BIOMOLECULAR ENGINEERING

Module I: Reaction kinetics and systems biology

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MODULE OVERVIEW

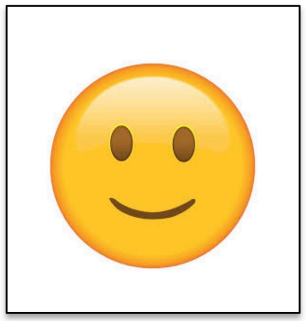
Reaction kinetics and systems biology (*Oliver Maclaren*)
[11 lectures/3 tutorials/2 labs]

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

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)

PEOPLE



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ASSESSMENT

Coursework: 60%, Exam: 40%

- Module 1 Coursework:
  - Computer lasb/assignments (2 x 2.5%)
  - Test (5%)
- Module 2 Coursework:
  - Lab assessments (6 labs, 35%)
  - Test (5%)
- Module 3 Coursework:
  - Assignment (10%)

SCHEDULE

Module 1 (4 weeks)

- Lectures: Monday (4-5pm), Tuesday (3-4pm), Wednesday (2-3pm)
- Tutorials: Thursday (1-2pm) - from week 2 on. Optional; do sheets in own time, can ask questions, discuss in tutorial.
- Labs: Friday (10am-1pm or 2-5pm) - weeks 2 and 3 only. Will form basis of computer assignments.

REFERENCES

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

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)*

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: energy, *mass*, momementum

Directional: entropy increases, *free energy decreases*

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

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 ⟶ Products

i.e.

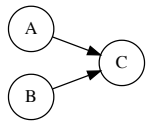
$$A + B \longrightarrow C$$

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

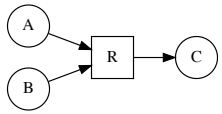
GRAPHICAL REPRESENTATIONS

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

Reaction graph:



Petri-net-style representation:



EXAMPLE

Steps

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

LAW OF MASS ACTION

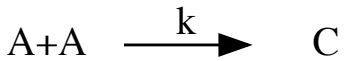
A 'law' in the way Newton's law of cooling, Hooke's law of elasticity, Ohm's law etc are 'laws' (i.e. not really!)

> *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*

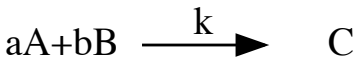
Can be motivated 'microscopically' or 'mechanistically' by collision theory.

MORE EXAMPLES

Example 1:



Example 2:



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?

COMPLICATIONS

- Units and dimensions
- Reversible/irreversible reactions

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

Bioeng 261 Lecture 1: Basic principles of Reaction modelling.

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

Key Principles

General

- conservation/symmetry { mass, energy, momentum
  - [possible]
- direction/asymmetry { entropy
  - [probable]
- constitutive* equations { Here: law of mass action
  - [actual]

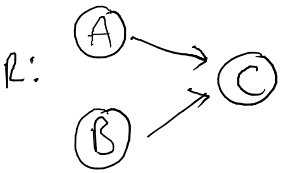
Specific

*→ like 'Hooke's law', $F = kx$
or Newton's gravitational 'law' $F = \frac{GmM}{r^2}$
→ think 'force'/'flux' modelling
→ valid for class of systems but not all.

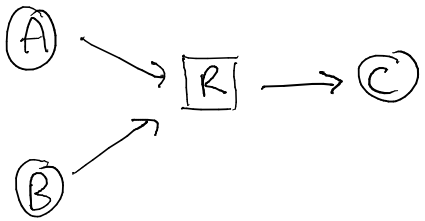
Graphical representations

Reactants $\xrightarrow{\text{rate}}$ Products

R: $A + B \xrightarrow{k} C$ Stoichiometric equation

R: 

Reaction graph

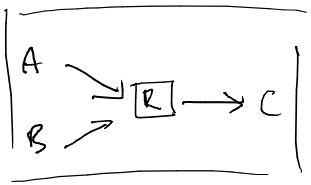


Petri Nets

(explicit rep. of reaction R with square node)

└ helpful to treat reaction as 'object' of interest itself

Example reaction



$$A + B \xrightarrow{k} C$$

1. Conservation of mass

Key: think in terms of the reaction itself:

each 'step', 1 A ↓, 1 B ↓, 1 C ↑

Flux $\tilde{J}$ of reaction

$$\frac{dA}{dt} = -\tilde{J}$$
$$\frac{dB}{dt} = -\tilde{J}$$
$$\frac{dC}{dt} = +\tilde{J}$$

note! (not eg $\tilde{J}/2$)

why $\tilde{J}$ & not J?
- fluxes!
  - see later

2. Specific model for flux $\tilde{J}$

'Law' of mass action.
- for 'elementary' reactions
- will assume more complex reactions built up from simple.

Intuition: collision theory

1A → collide = reaction → 1C

1B

rate ∝ number of collisions

$\approx$ number of A molecules × number of B molecules

$= A \times B$ (for $A+B \to C$)

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

↑

k: reaction rate 'constant'

[also depends on eg temperature
hotter = more collisions]

Finally....

$$\frac{dA}{dt} = -k \cdot A \cdot B$$

$$\frac{dB}{dt} = -k \cdot A \cdot B$$

$$\frac{dC}{dt} = +k \cdot A \cdot B$$

Mass action:

rate $\propto$ number of collisions of reactants

Order of reaction:

number of reactant collisions

Examples

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

(1.) R: $2A \rightarrow B$

[each step] $\downarrow 2A$, $\uparrow 1B$ } think in terms of reactions (each step)

(conservation (number per step)) $\left\{ \begin{array}{l} \frac{d[A]}{dt} = -2J \\ \frac{d[B]}{dt} = +J \end{array} \right\}$ & $J = \underbrace{k[A]^2}_{\text{rate}}$ ← chance of (collisions)

$$\Rightarrow \frac{d[A]}{dt} = -k \cdot \underbrace{2}_{=} \cdot [A]^{\underbrace{2}_{=}}; \quad \frac{d[B]}{dt} = k[A]^2$$

order = 2

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(4) $\frac{d[A]}{dt} = -a \cdot J$, $\frac{d[B]}{dt} = -b \cdot J$

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

order = $a + b$

Complications

- Units & dimensions
- Reversible/irreversible reactions

Amounts vs concentrations ?

Q: what is conserved ?

A: amount

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

$$= [A] \times V$$

($[A]$: concentration)

if Vol = constant

$$\frac{dA}{dt} = V \cdot \frac{d[A]}{dt} = \tilde{J} \quad \leftarrow \text{amount/time}$$

$$\frac{d[A]}{dt} = \frac{\tilde{J}}{V} = J \quad \leftarrow \text{amount/time·vol.} = \text{conc./time}$$

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

1 Molar (M) : 1 mol/litre : concentration

↳ typical: μM - mM

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

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

$$= \text{concentration}/\text{time} \quad (\text{eg } M/\text{sec})$$

Typically $\frac{d[A]}{dt} = J$ } we will often assume in terms of concentrations

But: Careful !

↳ eg if vol. is changing

Order & rate dimensions/units

1st order

$$J = k[A] = \frac{d[A]}{dt} \Rightarrow k : \frac{1}{\text{time}} \quad (\text{eg } \frac{1}{\text{sec}})$$

2nd order

$$J = k[A][B] = \frac{d[A]}{dt} \Rightarrow k : \frac{1}{\text{conc.}} \cdot \frac{1}{\text{time}} \quad (\text{eg } M^{-1}s^{-1})$$

We will look at Dimensional analysis & scaling 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 / glass spontaneously forming.

$A + B \xrightarrow{k_1} C$ vs $C \rightarrow A + B$ { there are special ways of encouraging one direction

Macroscopic irreversibility: [thermodyn.]

asymmetric { entropy increases (or Gibbs free energy decreases)

Example

Model $A + B \xrightarrow{k} C$

Really should be $A + B \underset{k_-}{\overset{k_+}{\rightleftharpoons}} C$ { key k_+ & k_- possible / BUT $k_+ \neq k_-$ probably

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 $k_- > k_+$

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

(there: same. But not always!)

Set (eg wait a long time)

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

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

if K_{eq} { large: $[A]_{eq}[B]_{eq} >> [C]_{eq}$
small: $[A]_{eq}[B]_{eq} << [C]_{eq}$

ie { $\xleftarrow{k_-}$ reverse dominates
$\xrightarrow{k_+}$ forward dominates

If $k_+ >> k_-$ we often approx as

$$A + B \xrightarrow{k} C$$

} 'favours' forward reaction*

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*Thermo: K_{eq} & hence ratios of rates k_+, k_- etc can be related to Gibbs free energy