

BIOMENG 261

TISSUE AND BIOMOLECULAR ENGINEERING

Module I: Reaction kinetics and systems biology

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LECTURE 7: SYSTEMS BIOLOGY AND LARGER SYSTEMS OF 'REACTIONS'

- Different formalisms and notation for building up models
- Systems biology and understanding complex systems
- Overview of signal transduction, gene regulation and metabolism
- Signal transduction modelling

MODULE OVERVIEW

Reaction kinetics and systems biology (*Oliver Maclarens*)

[11-12 lectures/3 tutorials/2 labs]

1. Basic principles: modelling with reaction kinetics [5-6 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: 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.

GENERALISED REACTIONS

We have been modelling key processes in terms of *reactions*

We can use reaction modelling as a *general modelling formalism* for many types of processes and many different levels

- Signal transduction
- Metabolic processes
- Gene regulation
- Etc

ROLE OF FORMALISMS

- Consistent formalisms make it easier to *bridge/connect various scales and process types*
- There are also *many other formalisms*; sometimes you want to combine many different model types for different processes

Here we continue using 'reactions' and ODEs as our basic modelling language

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SYSTEMS BIOLOGY?

Short version:

Traditional biology: Breakdown into pieces

Systems biology: Put it all back together!

Complementary approaches.

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NOTATION: NET FLUXES AND INDIVIDUAL FLUXES

Often useful to consider the *net flux for a given reaction = difference between forward and backward fluxes*. E.g.

$$J_1^{\text{Net}} = J_1 - J_{-1}$$

Another common notation is

$$J_1 = J_1^+ - J_1^-$$

Here J_1 corresponds to J_1^{Net} . *Careful!*

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KEY COMPONENTS: SIGNAL TRANSDUCTION, GENE REGULATION, METABOLISM

Helpful review:

Goncalves et al. (2013) 'Bridging the layers: towards integration of signal transduction, regulation and metabolism into mathematical models'. In: Mol. BioSyst.

On Canvas:

- You should read!
- You won't necessarily understand it all though!
- I won't assess you on it!

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METABOLISM

Short definition:

The consumption and production of chemical substances and energy to sustain life

- Catabolism: breakdown
- Anabolism: build up

Food → Life

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GENE REGULATION

Short definition:

Control of the levels of enzymes and other proteins (etc) via the regulation and control of transcription and translation of the genetic code

Cells control their 'production' of cell 'machinery' in response to the environment and other needs.

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SIGNAL TRANSDUCTION

Short definition:

How cells sense, translate and respond to external stimuli

i.e. chemical or physical 'signals'!

E.g.

- Ligands (signal molecules)
- Mechanical forces
- Concentration gradients

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TODAY: SIGNAL TRANSDUCTION EXAMPLE

Goal:

- *Exposure* to how more complex models are built up from the ideas introduced so far
- A few *extra details* on signal/membrane modelling
- Some *minor complications*:
 - Area vs volume concentrations and units
 - Varying enzyme levels and MM models

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SIGNAL TRANSDUCTION EXAMPLE

Example:

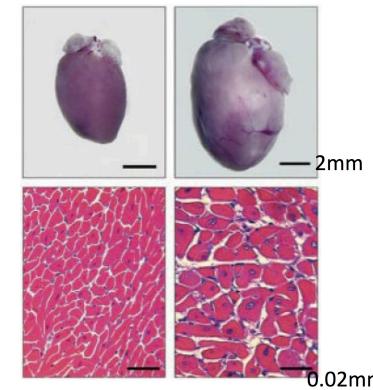
Cooling, Hunter and Crampin (2007) 'Modelling Hypertrophic IP3 Transients in the Cardiac Myocyte'. In: Biophys. J.

On Canvas:

- You should read!
- You won't necessarily understand it all though!
- I won't assess you on it!

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CARDIAC HYPERTROPHY



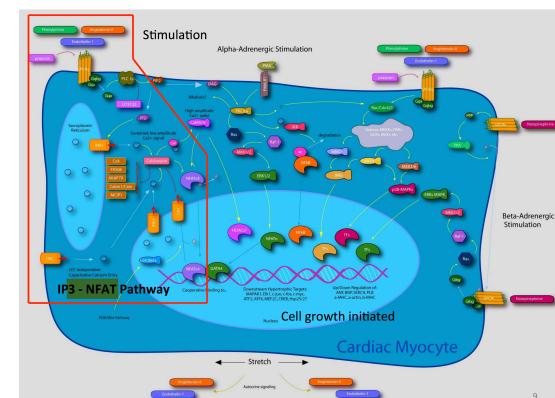
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CARDIAC HYPERTROPHY

- The heart's cells *adapt in response to the signalling of the rest of the body*.
- An example is the increase in cell volume: *cardiac hypertrophy*
 - Sometimes *non-pathological* adaptation (athletes, pregnancy)
 - Sometimes *pathological*, maladaptive and can lead to heart disease/failure

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CARDIAC HYPERTROPHY



Goal: convert to mathematics! See Cooling et al.

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EXTRA ELEMENT: SIGNALLING

Simple model (e.g. for IP₃ intracellular signalling molecule)

$$\frac{d[IP_3]}{dt} = J_{\text{prod}} - J_{\text{deg}}$$

where

$$J_{\text{prod}} = a$$

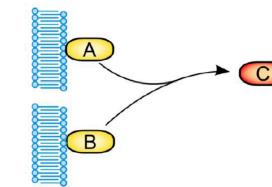
$$J_{\text{deg}} = k_{\text{deg}}[IP_3]$$

Here the production rate is treated as *controlled parameter*.

More complex model: see paper.

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TECHNICAL ISSUE I: MEMBRANE VS CYTOSOLIC CONCENTRATIONS



Remember: *amount is conserved, not concentrations*

- Need conversion factor between 'per area' and 'per volume' concentrations
 - See handout

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REMAINING PIECES

Use tools from *previous lectures!* E.g.

$$J_{11} = k_{f,11} \times P_g \times Ca - k_{r,11} \times P_{cg}$$

$$J_{12} = k_{f,12} \times P_{cg}$$

$$J_{13} = k_{f,13} \times P_g$$

$$J_{14} = \frac{k_{f,14} \times P_c \times PIP_2}{\left(\frac{k_{m,14}}{V_{pc}} + PIP_2 \right)}$$

$$J_{15} = \frac{k_{f,15} \times P_{cg} \times PIP_2}{\left(\frac{k_{m,15}}{V_{pc}} + PIP_2 \right)}$$

$$\frac{dP}{dt} = J_{13} - (J_9 + J_8)$$

$$\frac{dP_k}{dt} = J_9 - (J_{11} + J_{13})$$

$$\frac{dP_c}{dt} = J_8 + J_{12} - J_{10}$$

$$\frac{dP_g}{dt} = J_{10} + J_{11} - J_{12}$$

$$J_{16} = k_{f,16} \times IP_3$$

$$\frac{dIP_3}{dt} = (J_{14} + J_{15}) \times C_{pc} - J_{16}$$

$$\frac{dCa}{dt} = C_{pc} \times -1 \times (J_8 + J_{11})$$

Can you spot the various constitutive models we've seen?

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TECHNICAL ISSUE II: VARYING ENZYME LEVELS

Here our *enzyme levels are varying* (signalling affects transcription).

Typically *still use MM model but with current E level:*

$$v([S], [E]) = \frac{k[E][S]}{K_M + [S]}$$

instead of

$$v([S]) = \frac{kE_0[S]}{K_M + [S]}$$

(now also need model for [E] variations)

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Biomeng 261 Lecture 7

- Overview of 'systems biology'
 - ↳ Language & notation
 - ↳ Examples & challenges

Goal: we want to keep
'building up' (& down!) our
models to capture biological
complexity

Formalisms & Notations - what language?

We have been representing key
processes as 'reactions!'

↳ we can use more generally
as a modelling language
for many types of physical
processes & at multiple scales

Languages

- We will model many things
in reaction language that
aren't strictly chemical reactions
in the usual sense
- think 'networks of processes'
- examples include cell signalling,
metabolism & genetic regulation

Other languages exist!

See Goncalves et al (2013) on Canvas

Bridging the layers: towards integration of signal transduction, regulation and metabolism into mathematical models

Emanuel Gonçalves,^a Joachim Bucher,^b Anke Ryll,^c Jens Niklas,^b Klaus Mauch,^b Steffen Klamt,^c Miguel Rocha^d and Julio Saez-Rodriguez^{*a}

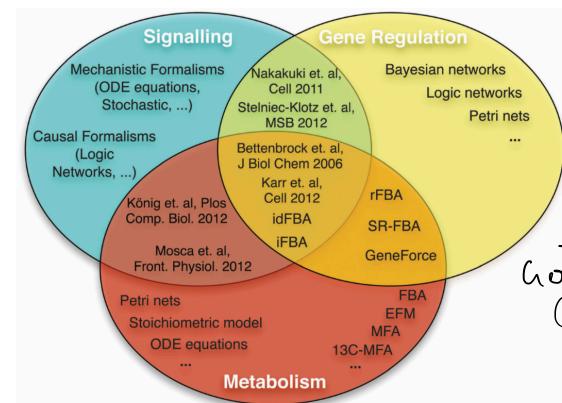
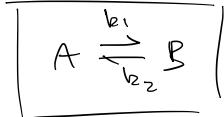


Fig 2.
Goncalves et al
(2013).

Note on notation :

Net fluxes & individual fluxes

Consider



→ we have been using J_1 & J_{-1} for forward & backward fluxes, respectively.

As we start to build up larger systems of reactions we often 'lump' together into

Net flux :

$$\boxed{J_1^{\text{net}} = J_1 - J_{-1}}$$

↑ ↑ ↑
net forward backward

confusingly, another common notation is

$$\boxed{J_1 = J_1^+ - J_1^-}$$

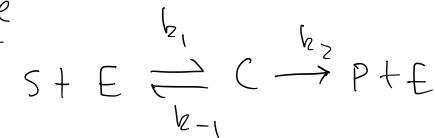
↑ ↑ ↑
ref forward backward

which?

→ Just be careful!

→ context should make it clear

Example



Notation $\frac{d[S]}{dt} = -J_1^{\text{net}} = -(J_1 - J_{-1})$
version 1.

$$\frac{d[E]}{dt} = -J_1^{\text{net}} + J_2^{\text{net}} = -(J_1 - J_{-1}) + J_2$$

etc

$$\& J_1^{\text{net}} = k_1[S][E] - k_{-1}[C] \text{ etc.}$$

Notation

version 2. $\frac{d[S]}{dt} = -J_1 = -(J_1^+ - J_1^-)$

$$\& J_1 = k_1[S][E] - k_{-1}[C]$$

etc.

→ if in doubt, be explicit!

'Systems' Biology ?

Traditional biology:

- break down into pieces
- 'Reductionist'

Systems biology:

- build back up into whole
- 'emergentist'
- Lots of 'interactions' & 'networks' etc.

'Engineering': best practice for building things up - modules, components, control, hierarchies etc.

These approaches complement each other

→ But engineers typically want to understand, manipulate & build 'wholes' or 'systems'

leads to synthetic biology
(design & build new biological systems)

Other issues

→ we end up building models that are as hard to understand as the original system!

Eg Babtie & Stumpf (2017) :

→ open challenges!

INTERFACE

rsif.royalsocietypublishing.org

Review



Cite this article: Babtie AC, Stumpf MPH.
2017 How to deal with parameters for whole-cell modelling. *J. R. Soc. Interface*
14: 20170237.
<http://dx.doi.org/10.1098/rsif.2017.0237>

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How to deal with parameters for whole-cell modelling

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Dynamical systems describing whole cells are on the verge of becoming a reality. But as models of reality, they are only useful if we have realistic parameters for the molecular reaction rates and cell physiological processes. There is currently no suitable framework to reliably estimate hundreds, let alone thousands, of reaction rate parameters. Here, we map out the relative weaknesses and promises of different approaches aimed at addressing this issue. While suitable procedures for estimation or inference of the whole (vast) set of parameters will, in all likelihood, remain elusive, some hope can be drawn from the fact that much of the cellular behaviour may be explained in terms of smaller sets of parameters. Identifying such parameter sets and assessing their behaviour is now becoming possible even for very large systems of equations, and we expect such methods to become central tools in the development and analysis of whole-cell models.

→ We'll look at some issues of parameter estimation etc in the next two lectures

→ first we'll look at building up models

Key pieces of the puzzle:

1. o Metabolism
2. o Signal transduction
3. o Gene regulation

1. Metabolism: Consumption & production of chemical substances & energy to sustain life

↳ Catabolism: Breakdown substances for energy & 'raw materials'

↳ Anabolism: Build up components of cells, e.g. proteins/enzymes etc

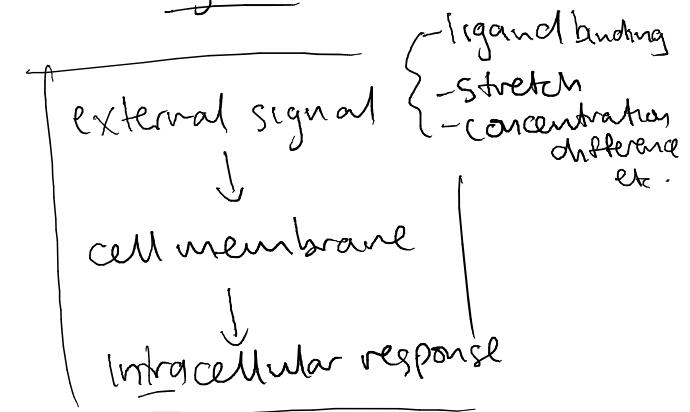
Short version: Food \rightarrow Life

Metabolic pathway:

→ series of steps in some metabolic reaction

2. Signal Transduction

↳ How cells sense, respond etc to external stimuli i.e. chemical or physical 'signals'



Signal transduction pathways & networks

- series of steps in particular signal transduction process
- involves interaction of series of proteins etc.
- think of in terms of 'modules' & 'components' making up larger 'circuits' & control systems

eg a 'switch' module

3. Genetic Regulation

L Control of the levels of enzymes & other proteins

via regulation & control of

- transcription ($DNA \rightarrow RNA$)
- translation ($mRNA \rightarrow Proteins$)

- similarly, can think of in terms of 'circuits' & 'control systems' with various (repeating) components

Systems biology again:

Metabolism, signal transduction & genetic regulation are all interconnected

Goal: understand (& build) complex bio systems

L still open problem of properly putting everything together } engineering job?
modularity etc

(→ we will continue with 'reaction' approach here)

Today: Signal transduction example

{ Use basic L1-L6 tools

{ Add simple stimulus → signal model

Few tech. details

[later: metab & genetic]

Goals: - exposure to general ideas of building models

- a few extra details on signal/membrane modelling

• Cardiac hypertrophy models

- cellular hypertrophy: type of adaptation to external signals/load

- Here: cells increase in volume

- risk factor for heart disease/failure

- At cellular level involves complex interaction of signal transduction pathways

- Cooling, Hunter & Crampin (2007)

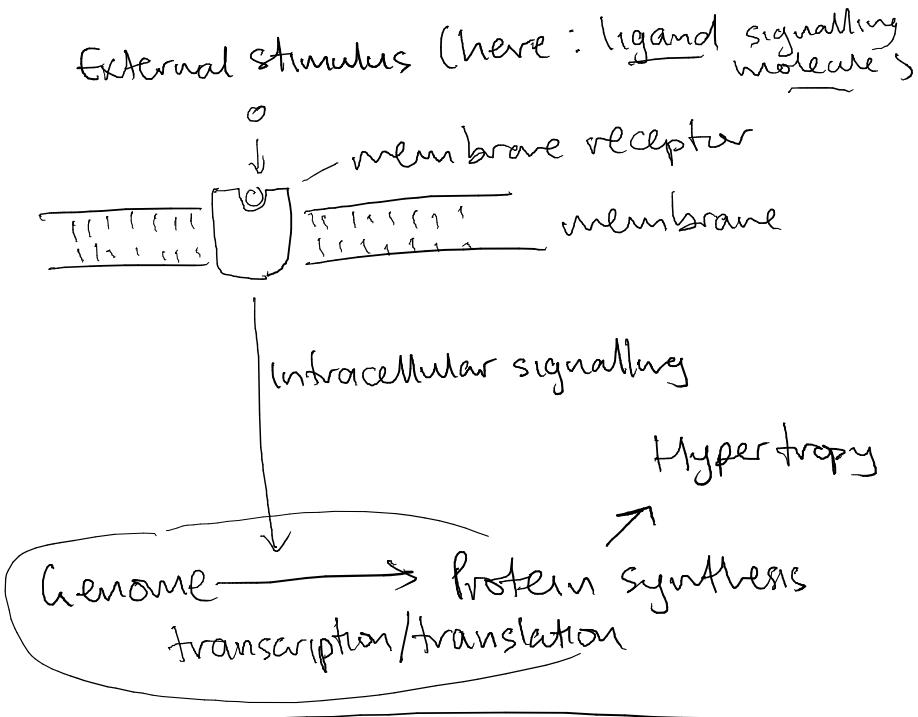
L paper (Biophys. J.). See canvas

L CellML model (cellml.org)

L IP3-calcineurin pathway stimulates NFAT → binds DNA cooperatively

- translate 'cartoon' to a mathematical model

Cartoon of Signal transduction pathway



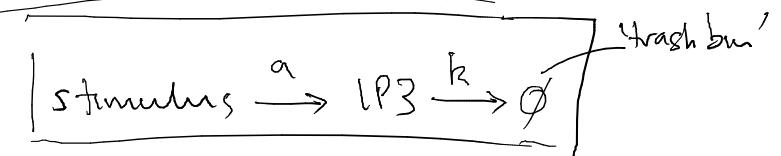
Hyper : excess
Trophy : nourishment

- Ligand: signalling molecule, binds to receptor
- Agonist: Ligand that stimulates activates
- Antagonist: Ligand that blocks the action of an agonist

Simple model of signal activation/decay

$$\frac{\text{production of intracellular signalling molecule}}{\text{extracellular signalling molecule level}} = f(\text{extracellular signalling molecule level})$$

$$\frac{\text{degradation of intracellular signalling molecule}}{\text{intracellular signalling molecule}} = \text{simple decay}$$



$$\frac{d[\text{IP}_3]}{dt} = J_{\text{prod}} - J_{\text{deg}}$$

$J_{\text{prod}} = \alpha = \text{external / control parameter}$

$$J_{\text{deg}} = k[\text{IP}_3]$$

→ here we can vary α & see response

→ can also model in more detail
see paper.

Combine signalling / stimulation
model....

with { Michaelis-Menten
Hill (cooperative)
Mass action

⇒ get [Signal transduction
model!]

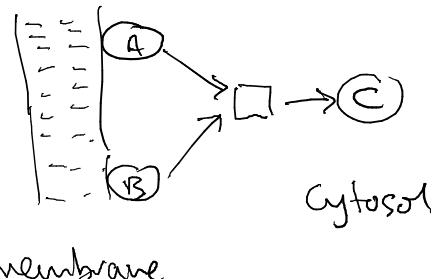
see Cooling, Hunter, Crampin (2007)

"Modelling hyperprophic IP₃
Transients in the Cardiac
Myocyte"

on canvas

Notes: Volume vs Area concentrations
of membranes

Some species/proteins are
membrane-bound &
some cytosolic:



⇒ need to account for
in converting from amounts
to concentrations

$$\frac{d[\text{Area} \times B]}{dt} = -\tilde{J}_i^{\text{net}} = \frac{\text{amount}}{\text{time}}$$

$$\frac{d[\text{Volume} \times C]}{dt} = +\tilde{J}_i^{\text{net}} = \frac{\text{amount}}{\text{time}}$$

define $\gamma = \frac{\text{area}}{\text{vol}}$ } conversion factor

$$J_i^{\text{net}} = \frac{\tilde{J}_i^{\text{net}}}{\text{vol}}$$

For now, assume vol constant
(not in general)

$$\frac{d[B]}{dt} = -\frac{1}{\text{area}} \times \tilde{J}_i^{\text{net}} = \frac{\text{vol}}{\text{area}} J_i^{\text{net}}$$

$$\frac{d[C]}{dt} = \frac{1}{\text{vol}} \tilde{J}_i^{\text{net}} = J_i^{\text{net}}$$

so

$$\begin{aligned} \frac{d[B]}{dt} &= -\frac{1}{\gamma} J_i^{\text{net}} \\ \frac{d[C]}{dt} &= J_i^{\text{net}} \end{aligned}$$

etc

Notes: Michaelis-Menten?

- The levels of enzymes
are varying!

- Can't just assume
 $[E] = E_0 - [C]$ etc.

- Simple approach: replace

$$J = \frac{k E_0 [S]}{K_m + [S]}$$

treat as empirical const.
eqn.
fit k, K_m

$$J = \frac{k [E] [S]}{K_m + [S]}$$

(+ need to model $[E]$ levels
depending on transcription
etc).