

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]

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 5: 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

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

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!*

SYSTEMS BIOLOGY?

Short version:

Traditional biology: Breakdown into pieces

Systems biology: Put it all back together!

Complementary approaches.

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!

METABOLISM

Short definition:

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

- Catabolism: breakdown
- Anabolism: build up

Food → Life

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

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.

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

SIGNAL TRANSDUCTION EXAMPLE

Example:

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

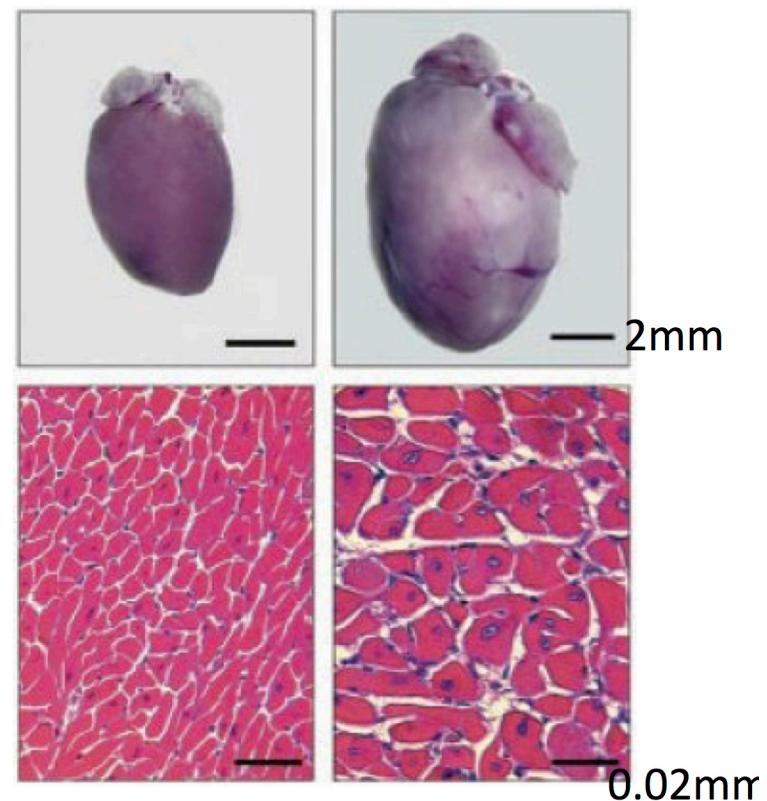
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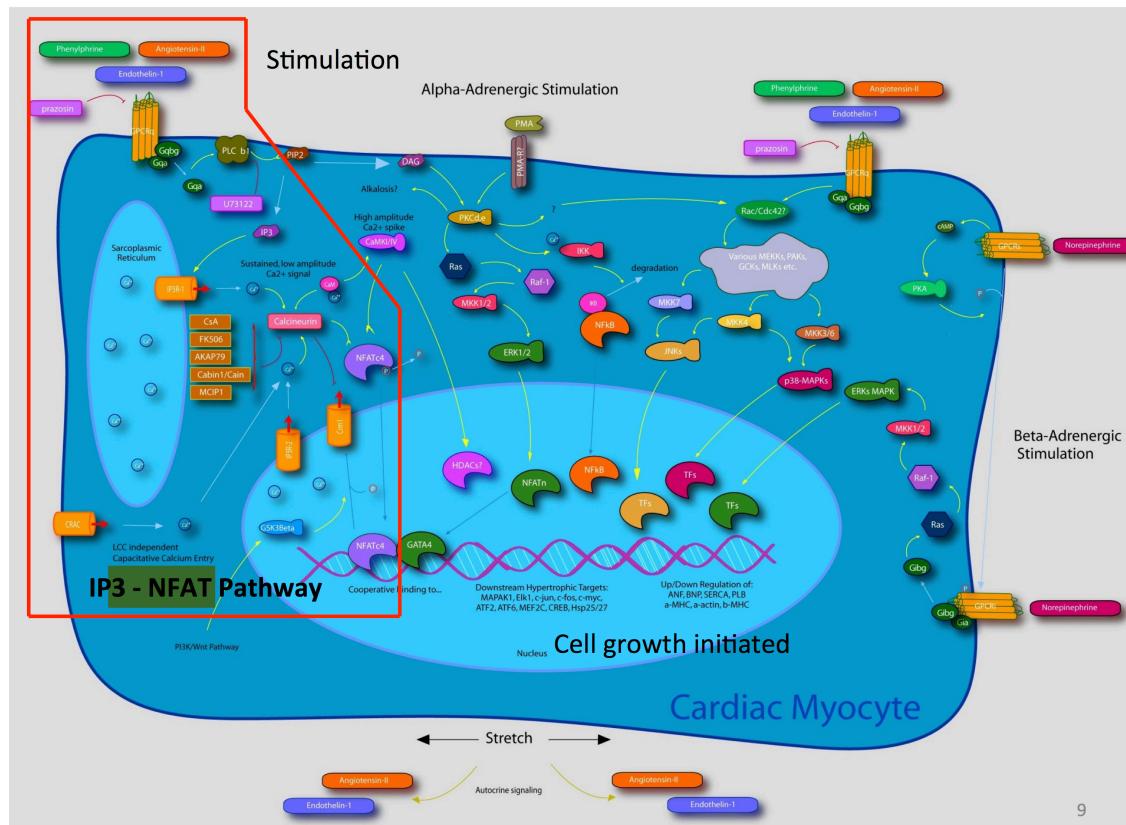
CARDIAC HYPERTROPHY

- 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

CARDIAC HYPERTROPHY



CARDIAC HYPERTROPHY



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Goal: convert to mathematics! See Cooling et al.

EXTRA ELEMENT: SIGNALLING

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

$$\frac{d[IP3]}{dt} = J_{\text{prod}} - J_{\text{deg}}$$

where

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

$$J_{\text{deg}} = k_{\text{deg}}[IP3]$$

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

More complex model: see paper.

REMAINING PIECES

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

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

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

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

$$J_{14} = \frac{k_{f,14} \times P_c \times PIP2}{\left(\frac{K_{m,14}}{C_{pc}} + PIP2 \right)}$$

$$J_{15} = \frac{k_{f,15} \times P_{cg} \times PIP2}{\left(\frac{K_{m,15}}{C_{pc}} + PIP2 \right)}$$

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

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

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

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

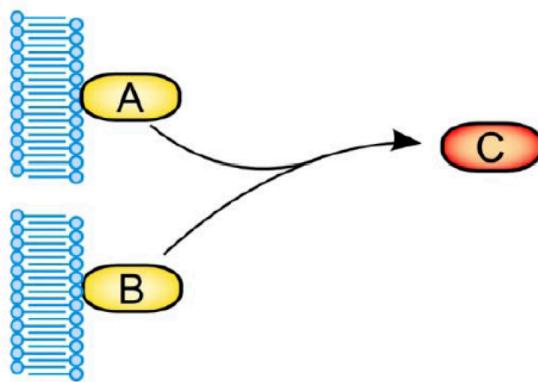
$$J_{16} = k_{f,16} \times IP3$$

$$\frac{dIP3}{dt} = (J_{14} + J_{15}) \times C_{pc} - J_{16}$$

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

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

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

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)