Bioeng 261 Lecture 5 Systems Biology. Signal Transduction

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

Formalisms & Notation – what language?

We have representing key process as "reactions"

→ quite a general modelling language
- Even things that aren't strictly chemical reactions can be modelled in these general terms } really, networks of processes
- applicable at multiple levels: eg we will use for cell signalling & for genetic regulation
- other modelling approaches exist though! Eg Boolean networks, Bayesian networks, Neural networks... people love 'networks'

Notation: Net fluxes & individual fluxes

Consider: $A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} B$

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

as we start to deal with larger systems we often want to 'lump' together into net flux:

$$J_1^{net} = J_1 - J_{-1}$$

Another common notation is

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

net — forward — backward

⇒ Careful! Will use either at diff. times, but will try to indicate which

Notation example

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C \xrightarrow{k_2} P + E$$

Notation v.1.

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

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

$$\vdots \quad \text{etc} \quad [\text{exercise!}]$$

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

$$\text{etc.}$$

Notation v.2.

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

$$\vdots$$

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

$$\text{etc} \quad [\text{exercise!}]$$

Note: J_1 here is J_1^{net} above etc.
⇒ Just be explicit which.

'Systems' Biology?

Traditional biology:
- break whole down into pieces
- 'Reductionist'

Systems biology:
- build back up into whole
- 'Emergentist'
- Lots of 'networks'
- 'modules', 'components', control, hierarchies & reuse etc ('engineering')

⇒ These approaches complement each other

But Engineers typically want to understand, manipulate & build 'wholes'

leads to 'synthetic' biology
→ design & build new biological systems

Key pieces of the puzzle:

1. Metabolism
2. Signal transduction
3. Gene regulation

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1. **Metabolism**: Consumption & production of chemical substances & energy to sustain life
   - Catabolism: Breakdown substances for energy & 'raw materials'
   - Anabolism: Build up components of cells, eg proteins/enzymes etc

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Short version: **Food → Life**

Metabolic **pathway**:
→ series of steps in some metabolic reaction

2. Signal Transduction

- How cells sense, respond etc to external stimuli ie chemical or physical 'signals'

external signal (- ligand binding, - stretch, - concentration difference etc.)
↓
cell membrane
↓
intracellular response

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

- Control of the levels of enzymes & other proteins via regulation & control of
  - transcription (DNA → RNA)
  - translation (mRNA → Proteins)
- Similarly, can think of in terms of 'circuits' & 'control systems' with various (repeating) components

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Systems biology again:
Metabolism, signal transduction & genetic regulation are all **interconnected**

Goal: understand (& build) complex bio systems

- 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–L4 tools
- Add simple stimulus → signal model
- Few tech. details

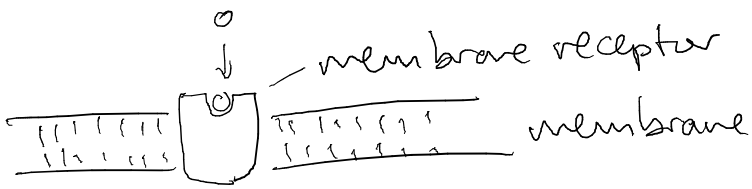
[later: metab. & genetic]

Goals:- exposure to general ideas of building models
- a few extra details on signal/membrane modelling

- Cardiac hypertrophy models
  - cellular hypertrophy: type of adaption 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)
    - paper (Biophys. J.). See Canvas
    - CellML model (Cellml.org)
    - IP3–calcineurin pathway stimulates NFAT → binds DNA cooperatively
  - translate 'cartoon' to a mathematical model →

Cartoon of signal transduction pathway

External stimulus (here: ligand signalling molecule)



Intracellular signalling

Hypertrophy

Genome → Protein synthesis
transcription/translation

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

production of intracellular signalling molecule = f(extracellular signalling molecule level)

+

degradation of intracellular signalling molecule = simple decay

stimulus $\xrightarrow{a}$ IP3 $\xrightarrow{k}$ $\emptyset$ 'trash bin'

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

$J_{prod} = a$ = external/control parameter

$J_{deg} = k[IP3]$

→ here we can vary 'a' & 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!**

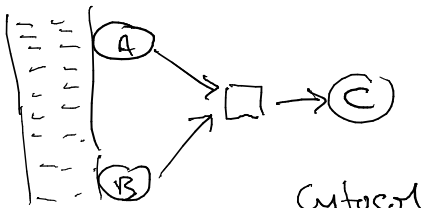
See Cooling, Hunter, Crampin (2007)

"Modelling hypertrophic IP3 Transients in the Cardiac Myocyte"

on Canvas

Notes: Volume vs Area concentrations & membranes

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



⇒ need to account for in converting from amounts to concentrations

$$\frac{d[\text{Area} \times B]}{dt} = -\tilde{J}_1^{net} = \frac{\text{amount}}{\text{time}}$$

$$\frac{d[\text{volume} \times C]}{dt} = +\tilde{J}_1^{net} = \frac{\text{amount}}{\text{time}}$$

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

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

For now, assume vol constant (not in general)

$$\frac{d[B]}{dt} = \frac{-1}{\text{area}} \times \tilde{J}_1^{net} = \frac{\text{vol}}{\text{area}} J_1^{net}$$

$$\frac{d[C]}{dt} = \frac{1}{\text{vol}} \tilde{J}_1^{net} = J_1^{net}$$

so

$$\boxed{\begin{aligned} \frac{d[B]}{dt} &= -\frac{1}{\gamma} J_1^{net} \\ \frac{d[C]}{dt} &= J_1^{net} \end{aligned}}$$

← just use conversion

etc

Notes: Michaelis–Menten?

- The levels of enzymes are varying!

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

- Simple approach: replace

$$J = \frac{kE_0[S]}{K_M + [S]}$$

with variable

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

treating as empirical constant. eqn. → fit k, K_M

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