Biomeng 261 Lecture 07 2017

- Parameter estimation cont'd
  - Challenges – large number of parameters
    – trade-offs!
- Example: Metabolic models & estimation of these
- Approach: Flux Balance Analysis (FBA) (new) } · constraints · linear alg. · optimisation

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Interesting paper (just published):

> 'How to deal with parameters for whole-cell modelling'
> Babtie & Stumpf (2017)

Quotes: (Babtie & Stumpf 2017)

'currently no suitable framework to reliably estimate hundreds, let alone thousands, of reaction rate parameters'

→ see paper/slides

Trade-offs involved.

Goals: Again, Systems Biology

> Want to tackle increasingly larger scale* / complex systems

* (ie lots of parameters)

Example: Metabolic Models

Recall: Metabolism (cellular)

> 'all the chemical processes keeping the cell alive'

→ lots!

Many 'pathways'

- series of enzyme-catalysed reactions
- each lead to breakdown (catabolism) or synthesis (anabolism) of specific metabolites (subst. formed as part of or necessary for metabolism)
- they interact too!

Examples

- see slides
- Key point: large systems
  - even 'simple' red blood cell model
    - ~100 ODEs!
    - each with many parameters
- Parameters often unknown / to be estimated
  - systematic search infeasible
  - 'non-identifiable': no unique 'best' set } 'ill-posed'

Approaches

L6
- search for smaller sets of important param.
  - complexity penalty
  - see eg Babtie & Stumpf

Today
- Try something else!

Babtie & Stumpf (2017)

'Perhaps the best established [large-scale cell models] are metabolic models... based around flux balance analysis (FBA)...'

→ makes whole genome-scale models feasible

→ comes at a cost (trade-offs!)

↳ only considers overall eg mass balances of reactions (stoichiometry) – no constitutive eq^{n}s.

(Can also include some overall energetic/thermodynamic info too)

↳ primarily steady-state-based

Simple motivating example

Consider the system

$$A \underset{J_1^-}{\overset{J_1^+}{\rightleftharpoons}} B, \quad B \underset{J_2^-}{\overset{J_2^+}{\rightleftharpoons}} C, \quad C \underset{J_3^-}{\overset{J_3^+}{\rightleftharpoons}} A$$

In terms of net fluxes, ie $J_i = J_i^+ - J_i^-$, we can write

$$A \xrightarrow{J_1} B, \quad B \xrightarrow{J_2} C, \quad C \xrightarrow{J_3} A$$

where $\xrightarrow{J_1}$ represents $\underset{J_1^-}{\overset{J_1^+}{\rightleftharpoons}}$ etc.

Conservation of mass is then

$$\frac{d[A]}{dt} = -J_1 + J_3$$

$$\frac{d[B]}{dt} = +J_1 - J_2$$

$$\frac{d[C]}{dt} = +J_2 - J_3$$

Now, write this using matrices/vectors

define:

$$\bar{C} = \begin{bmatrix} [A] \\ [B] \\ [C] \end{bmatrix}, \quad \frac{d\bar{C}}{dt} = \begin{bmatrix} \frac{d[A]}{dt} \\ \frac{d[B]}{dt} \\ \frac{d[C]}{dt} \end{bmatrix}$$

$\bar{C}$: concentrations vector

$$\bar{J} = \begin{bmatrix} J_1 \\ J_2 \\ J_3 \end{bmatrix}$$

$\bar{J}$: net flux vector

(overbar: vector, underbar: matrix)

$\Rightarrow$ gives

$$\frac{d\bar{C}}{dt} = \begin{bmatrix} -1 & 0 & +1 \\ +1 & -1 & 0 \\ 0 & +1 & -1 \end{bmatrix} \bar{J}$$

defines matrix $\underline{S}$:

$$\Rightarrow \boxed{\frac{d\bar{C}}{dt} = \underline{S}\,\bar{J}}$$

note: (also use v instead of J sometimes)

Stoichiometric matrix $\underline{S}$

Given M species & N reactions, each of the form

$$\alpha_{1j} C_1 + \alpha_{2j} C_2 + \cdots \xrightarrow{J_j\ \text{net}} \beta_{1j} C_1 + \beta_{2j} C_2 + \cdots$$

($\alpha_{1j} C_1 + \alpha_{2j} C_2$: lose; $\beta_{1j} C_1 + \beta_{2j} C_2$: gain)

$\Rightarrow$ define the **Stoichiometric Matrix**

$$\underline{S} = \begin{array}{c} \\ C_1 \\ C_2 \\ \vdots \\ C_M \end{array} \begin{array}{c} \begin{array}{cccc} J_1 & & & J_N \end{array} \leftarrow J_s \text{ just to help fill in matrix} \\ \begin{bmatrix} \beta_{11}-\alpha_{11} & & & \beta_{1N}-\alpha_{1N} \\ & & & \\ & & \beta_{ij}-\alpha_{ij} & \\ & & & \\ \beta_{M1}-\alpha_{M1} & & & \beta_{MN}-\alpha_{MN} \end{bmatrix} \end{array}$$

C_s just to help fill in matrix

Note: $+\beta_j - \alpha$

$\Rightarrow$ sign determined by choice of sign for net flux.

Example: 3rd reaction in some system is

$$\alpha_1 A + \alpha_3 C \xrightarrow{J_3} \beta_1 A + \beta_4 D + \beta_8 H$$

(lose: $\alpha_1 A + \alpha_3 C$; gain: $\beta_1 A + \beta_4 D + \beta_8 H$)

$$S = \begin{array}{c} \\ A \\ B \\ C \\ D \\ \vdots \\ H \end{array} \begin{bmatrix} J_3 \\ \beta_1 - \alpha_1 \\ 0 \\ -\alpha_3 \\ \beta_4 \\ \vdots \\ \beta_8 \end{bmatrix}$$

↑ 3rd reaction.

Example:

$$C \xrightarrow{J_1} A + D$$

$$A + 3D \xrightarrow{J_2} B + E$$

$$B \xrightarrow{J_3} D$$

} exercise! determine S.

Mathematical Framework PI.

Note: we are working in terms of pure fluxes ie conservation of mass

→ No constitutive eqns

→ No rate parameters

Problem: 'closure'

→ can't connect J back to concentrations

ie NO ODEs of form $\frac{dC}{dt} = f(C)$ ← don't know functional form.

'Solution': just consider steady states & treat fluxes as the unknowns to be det.

Steady state flux balance analysis (FBA)

- Makes some sense when thinking about overall metabolism in particular (hence popular in this area)
- only need stoichiometry (mass balance)
- often available eg metabolic network maps

⇒ **New goal**

Solve $\underline{S}\,\bar{J} = \bar{0}$

for fluxes J ← now unknowns of interest

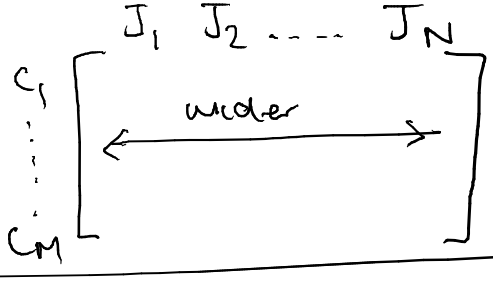
(not rate constants)

No free lunch: difficulties

- usually more reactions than metabolites (concentrations)

→ **remember, the reaction fluxes are the unknowns**

- often don't know all metabolites involved



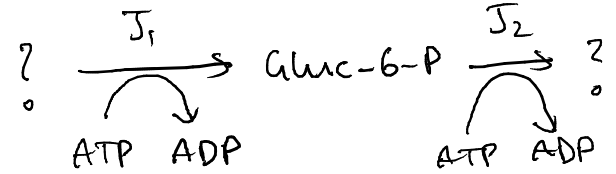
More columns (unknowns J) than rows (equations)

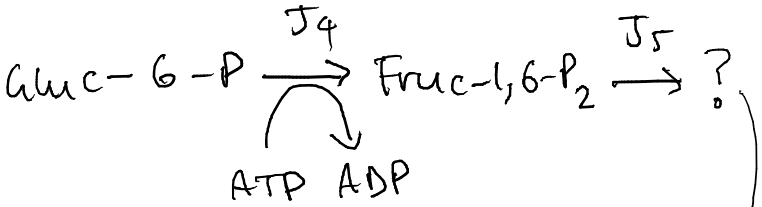
⇒ typically underdetermined

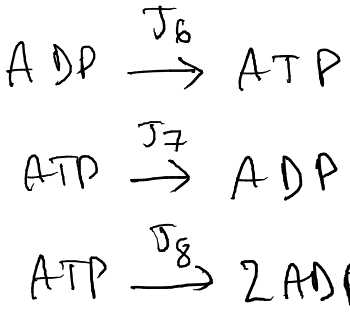
ie multiple solutions for J

(Makes sense: conservation: possible constitutive: actual)

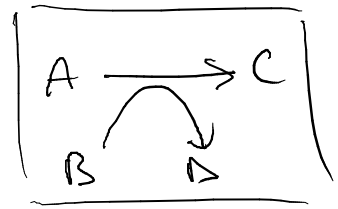
Example: Glycolysis (partial)



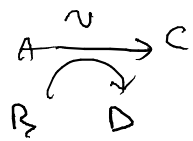




allow 'unknown' metabolites → no row but reaction (col) is included

Note 

is just $A + B \xrightarrow{J} C + D$

also often see 

ie v instead of J.

$$S = \begin{pmatrix} 1 & -1 & -1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 \\ -1 & -1 & 0 & -1 & 0 & 1 & -1 & -1 \\ 1 & 1 & 0 & 1 & 0 & -1 & 1 & 2 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$
← Gluc-6P
← Fruc-6P
← Fruc-1,6-P_2
← ATP
← ADP
← AMP

6 rows, 8 cols
↳ unknowns. (J)

unknowns > eq^{n}s !

$$S\bar{J} = \bar{0}$$

2 sol^{n}s: (at least)

$$\bar{J} = \begin{pmatrix} 1 \\ 1 \\ 0 \\ 0 \\ 0 \\ 2 \\ 0 \\ 0 \end{pmatrix} \quad \text{or} \quad \bar{J} = \begin{pmatrix} 0 \\ -1 \\ 1 \\ 1 \\ 1 \\ 0 \\ 0 \\ 0 \end{pmatrix}$$

"Non trivial null space"
↳ set of solutions x to $Ax = 0$
→ next time!

non-unique soln