BIOMENG 261

TISSUE AND BIOMOLECULAR ENGINEERING

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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 7: PARAMETER ESTIMATION CONTINUED (FBA)

- Parameter estimation continued
- Challenges: extending to large-scale/many parameter systems
- Example: Metabolism models
- Different approach: Flux balance analysis (FBA)

HOW TO DEAL WITH PARAMETERS FOR WHOLE-CELL MODELLING?

INTERFACE

rsif.royalsocietypublishing.org

Review

Check for updates

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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 redressing 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.

EXAMPLE: METABOLIC MODELS

Recall: *metabolism*

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

- Catabolism: breakdown
- Anabolism: build up

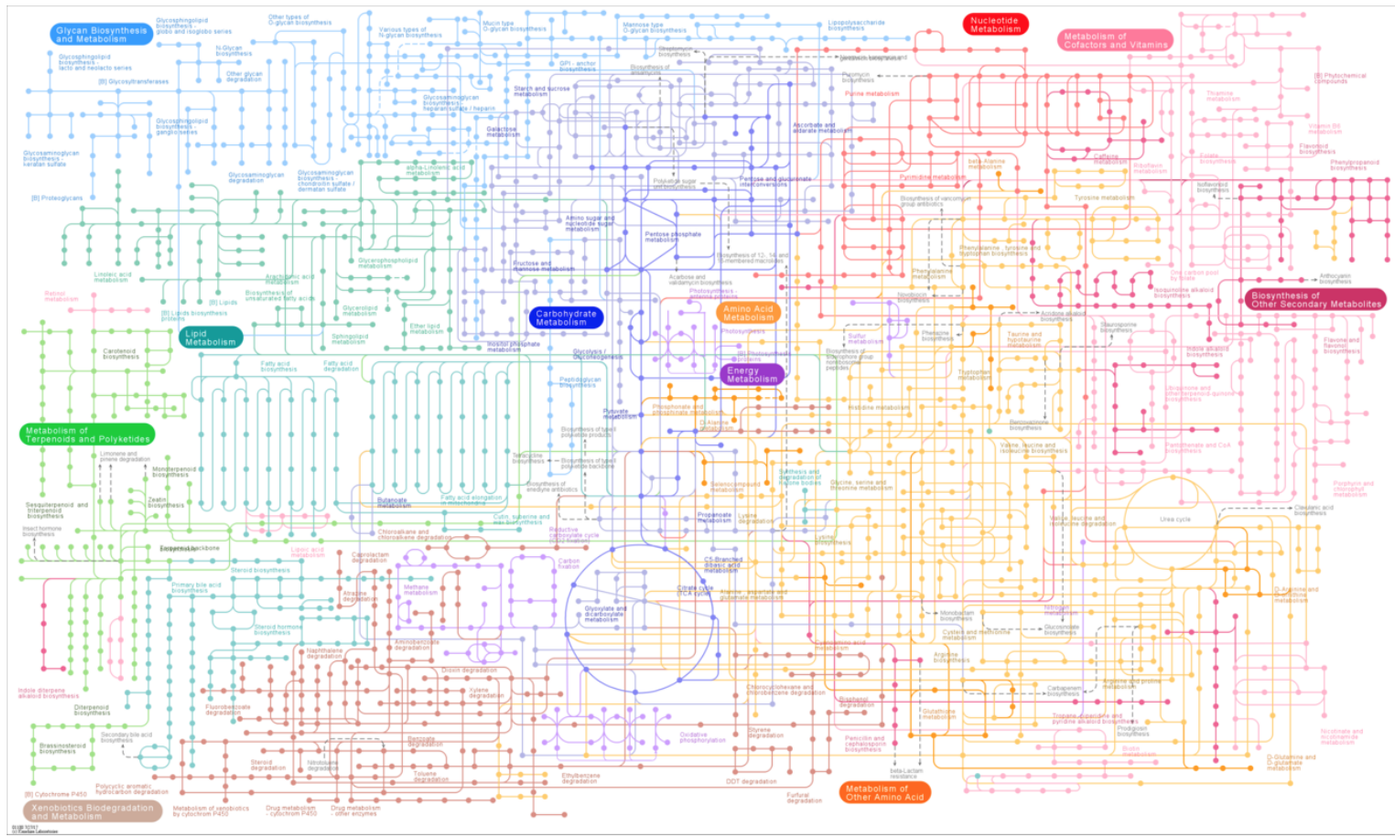
Food ⟶ Life

METABOLIC MODELS AS NETWORKS

Usually viewed as a large network of interacting pathwways

Can reconstruct via genome sequencing

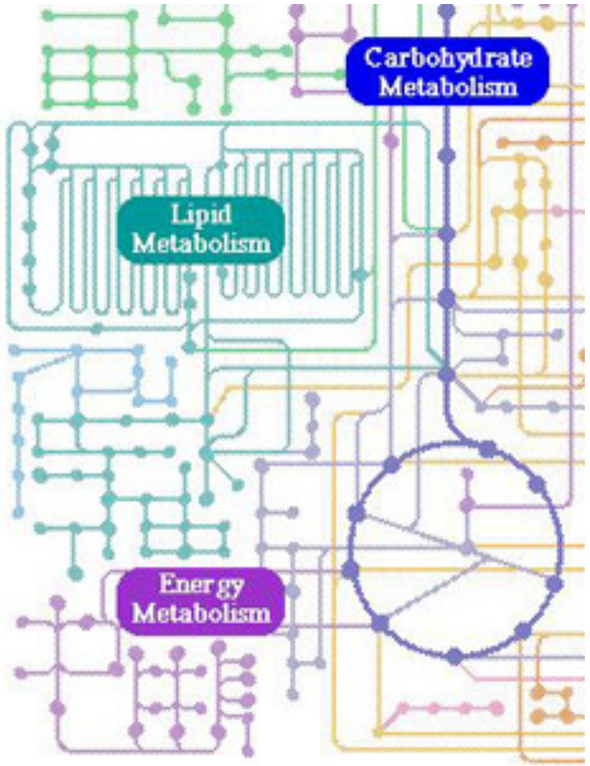
EXAMPLE METABOLIC MODELS/NETWORKS



From: http://www.genome.jp/kegg-bin/show_pathway?map01100

EXAMPLE METABOLIC MODELS/NETWORKS

Zoomed in:



APPROACHES

- *Full dynamic model* and search for smaller sets of important parameters (e.g. introduce complexity trade-off)
  - See previous lecture. *Difficult to scale up* to this size!
- *Try something else!*

FLUX BALANCE ANALYSIS

More from Babtie and Stumpf (2017):

present in a system. In cell biology, for example, there are now numerous attempts at modelling aspects of metabolism, gene regulation and signalling at cellular level [17–24]. Perhaps the best established are metabolic models, where a powerful set of tools, based around *flux balance analysis* (FBA) [25], allows us to explore metabolic phenotypes *in silico* at a genomic level for an increasing range of organisms (and some individual cell types) [24,26,27]. However, such models are stoichiometric and thus give us information about biochemical reaction schemes and fluxes, but not details about the system dynamics.

MOTIVATING EXAMPLE

Consider

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

or, equivalently in terms of *net* fluxes:

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

where $J_1 = J_1^+ - J_1^-$ etc, and the arrows represent *net* fluxes

MATRIX/VECTOR FORM

Derivation: see handout.

Result:

$$\frac{d\mathbf{C}}{dt} = \mathbb{S}\mathbf{J}$$

where $\mathbf{C}$ is a *vector* of concentrations/metabolites, $\mathbf{J}$ is a *vector* of fluxes and...$\mathbb{S}$ is the...

STOICHIOMETRIC MATRIX $\mathbb{S}$

Given M species/metabolites and N reactions, each of the form

$$\alpha_{1j}C_1 + \alpha_{2j}C_2 + \ldots \xrightarrow{J_j} \beta_{1j}C_1 + \beta_{2j}C_2 + \ldots$$

(lose) (gain)

STOICHIOMETRIC MATRIX

...we write these as a *matrix*

$$\mathbb{S} = \begin{bmatrix} \beta_{11} - \alpha_{11} & \dots & \beta_{1N} - \alpha_{1N} \\ \dots & \beta_{ij} - \alpha_{ij} & \dots \\ \beta_{M1} - \alpha_{M1} & \dots & \beta_{MN} - \alpha_{MN} \end{bmatrix}$$

Note

- Rows: species
- Columns: fluxes
- Entries: gain minus loss (stoichiometric coefficients)

MATHEMATICAL FRAMEWORK OF FLUX BALANCE ANALYSIS

Here we see how far we can get with just mass balance, i.e. *without constitutive equations*.

Constitutive equations allow us to write $\mathbf{J} = \mathbf{J}(\mathbf{C}; \mathbf{k})$ and hence, given rate parameters, get a *closed* system of equations

$$\frac{d\mathbf{C}}{dt} = f(\mathbf{C}; \mathbf{k})$$

Without constitutive equations *we don't have a closed system of ODE equations* to solve!

MATHEMATICAL FRAMEWORK OF FLUX BALANCE ANALYSIS

Instead, we aim to solve the *steady-state* equation

$$\mathbb{S}\mathbf{J} = \mathbf{0}$$

for the vector of *fluxes* $\mathbf{J}$, *here treated as unknown*.

Note:

- No consitutive equations/no rate parameters involved here.
- We don't need to know the metabolite concentrations, just solve for fluxes

NO FREE LUNCH

We only get *steady-state flux* information.

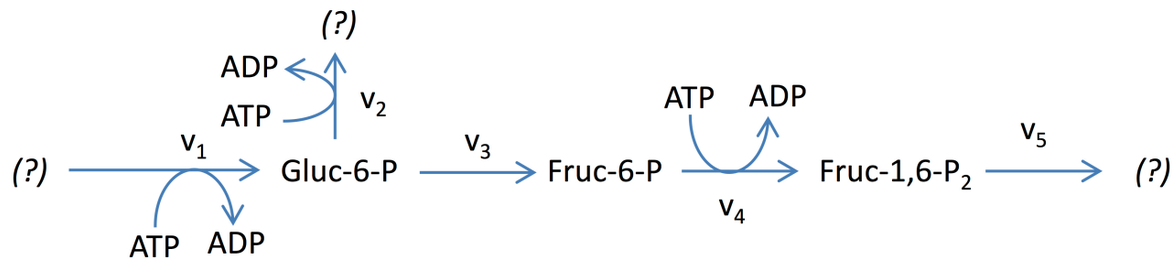
Furthermore, for a given metabolic network there are typically more reactions than species/metabolites

More columns (unknowns) than rows (equations)

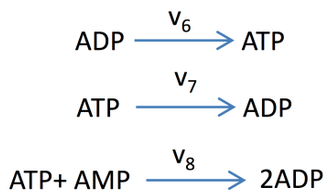
The problem is *underdetermined*, i.e. there are typically *multiple solutions*.

There is a non-trivial *null space* (see next lecture).

EXAMPLE



and



See handout.