

BIOMENG 261

TISSUE AND BIOMOLECULAR ENGINEERING

Module I: Reaction kinetics and systems biology

Oliver Maclaren
oliver.maclaren@auckland.ac.nz

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 8: FLUX BALANCE ANALYSIS CONTINUED

- Flux balance/constraint-based analysis continued
- Null spaces and spans (linear algebra)
- Geometry of constraints
- Extra constraints
- Optimality conditions (linear programming)

WHAT IS FLUX-BASED ANALYSIS?

Orth et al. (2010) in Nature Biotechnology:

What is flux balance analysis?

Jeffrey D Orth, Ines Thiele & Bernhard Ø Palsson

Flux balance analysis is a mathematical approach for analyzing the flow of metabolites through a metabolic network. This primer covers the theoretical basis of the approach, several practical examples and a software toolbox for performing the calculations.

(see Canvas)

WHAT IS FLUX-BASED ANALYSIS?

Orth et al. (2010) in Nature Biotechnology:

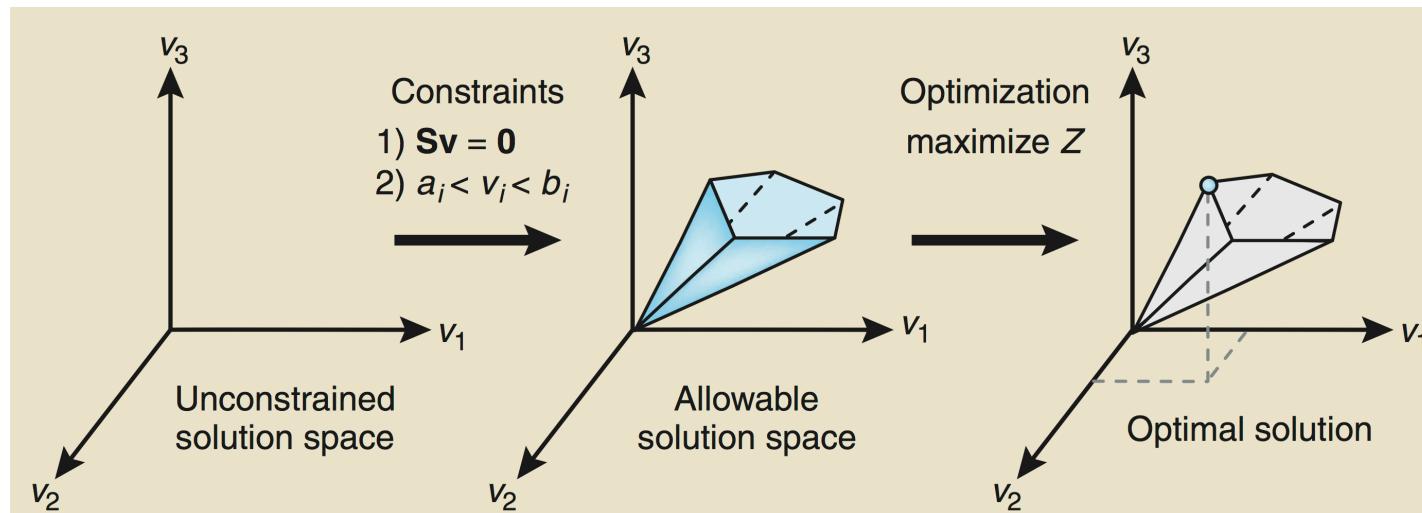


Figure 1 The conceptual basis of constraint-based modeling. With no constraints, the flux distribution of a biological network may lie at any point in a solution space. When mass balance constraints imposed by the stoichiometric matrix \mathbf{S} (labeled 1) and capacity constraints imposed by the lower and upper bounds (a_i and b_i) (labeled 2) are applied to a network, it defines an allowable solution space. The network may acquire any flux distribution within this space, but points outside this space are denied by the constraints. Through optimization of an objective function, FBA can identify a single optimal flux distribution that lies on the edge of the allowable solution space.

RECALL: FLUX BALANCE ANALYSIS

Instead of the dynamic (ODE) problem, 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*.

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

RECALL: FLUX BALANCE ANALYSIS

For a given metabolic network there are *typically* (not always) more reactions than species/metabolites i.e.

*More columns (unknowns) than rows
(equations)*

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

There is a non-trivial *null space*.

NULL SPACE?

For a matrix \mathbb{A} the *null space* is just the set of solutions to the zero problem

$$\mathbb{A}\mathbf{x} = \mathbf{0}$$

i.e. here

$$N(\mathbb{S}) = \{\mathbf{x} \mid \mathbb{S}\mathbf{x} = \mathbf{0}\}$$

Example.

SPAN?

The *span* of a set of vectors is just the set of all linear combinations of these, i.e. the *hyperplane* these define.

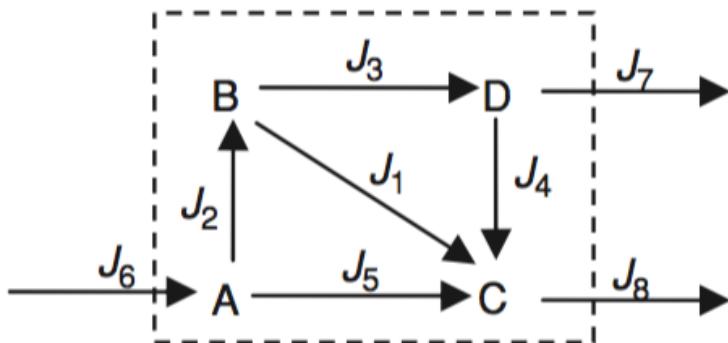
Here we have

$$N(\mathbb{S}) = \text{span}\{\text{indep. solutions of } \mathbb{S}\mathbf{x} = \mathbf{0}\}$$

Example.

BOUNDARIES, INTERNAL FLUXES AND INEQUALITY VS EQUALITY CONSTRAINTS

We often want to 'draw boundaries' around a 'system' of interest. We can either *include* these boundary fluxes as usual or treat them like '*slack*' variables for *inequality* constraints



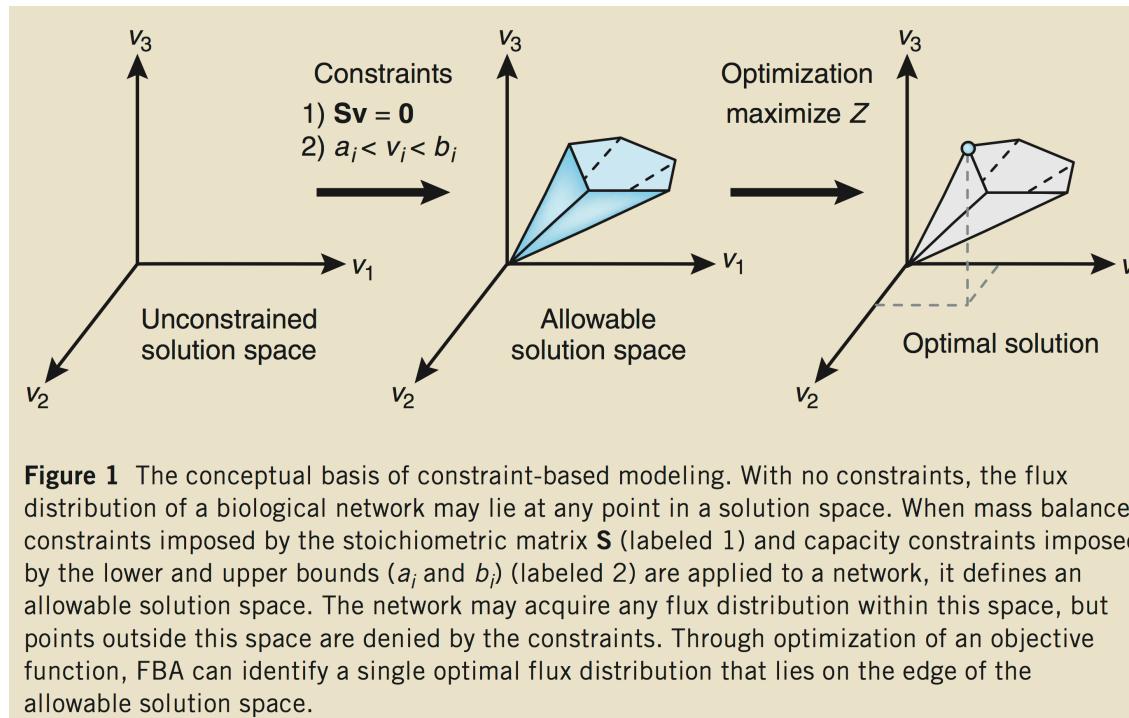
BOUNDARIES, INTERNAL FLUXES AND INEQUALITY VS EQUALITY CONSTRAINTS

- *Equality* constraints $\mathbb{S}\mathbf{J} = \mathbf{0}$ define *hyperplanes* in the space of *all fluxes* (including boundary etc fluxes).
- *Inequality* constraints $\mathbb{S}\mathbf{J} \geq \mathbf{0}$ define *polyhedra* in the *reduced* set of fluxes (e.g. internal only).

Equivalent, given proper care, but just be aware of which.

BOUNDARIES, INTERNAL FLUXES AND INEQUALITY VS EQUALITY CONSTRAINTS

Implicit inequality constraints give the polyhedra seen in:



UNIQUENESS? CONSTRAINT-BASED ANALYSIS

Clearly, there are multiple compatible solutions. To explore these further we can

- Add *bounds* (capacity constraints) on fluxes
- Add *directional* constraints (from thermodynamics)
- Look for special '*optimal*' solutions (e.g. maximum ATP production)

We say we are carrying out a *constraint-based analysis*...for obvious reasons! (FBA is a particular type of constraint-based analysis).

EXAMPLE

See handout.

GENERAL OPTIMISATION FRAMEWORK

We can formulate our problem as

$$\min z = \mathbf{c}^T \mathbf{J}$$

subject to

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

$$l_i \leq J_i \leq u_i$$

for $i = 1, \dots, N$ and a vector \mathbf{c} of scalar 'costs' (weights), i.e. a

*linear programming optimisation problem
(see EngSci OpsRes courses!)*

WHAT DO I NEED TO BE ABLE TO DO?

- Given a network, find \mathbb{S}
- Find the nullspace for a simple \mathbb{S} (see handout)
- Describe/list some constraints or conditions that we might add to explore our null space and find special solutions
- Write down an optimisation problem given a problem description
- Solve a simple optimisation problem