METAPOGRAMME DIGIT-BIO

Concepts maths pour comprendre le vivant - Séance 2

Battle de méthodes

La modélisation du métabolisme : modèle sous contraintes vs modèle EDO

C. Baroukh – W. Liebermeister

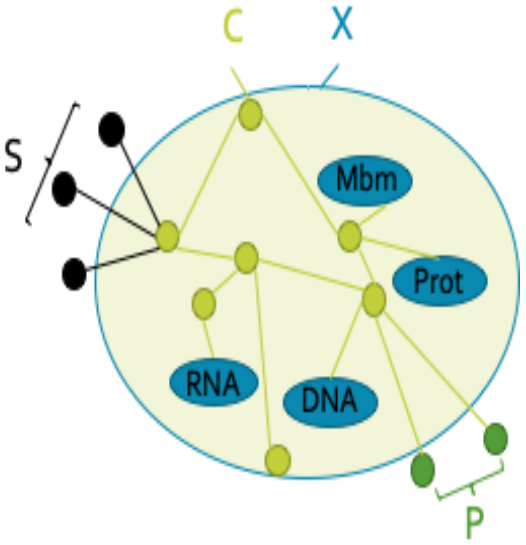
Context and metabolic networks

Metabolism

•Set of biochemical reactions that synthesise molecules that constitute life:
DNA, RNA, proteins, membrane lipids, cofactors, vitamines, hormones, etc…

•Substrates (S) are converted into numerous intermediate metabolites (C) to synthesise biomass components or to be excreted (P)

•Substrates must contain all the atoms necessary for life: carbon, oxygen, hydrogen, nitrogen, sulfur, phosphate, magnesium, …



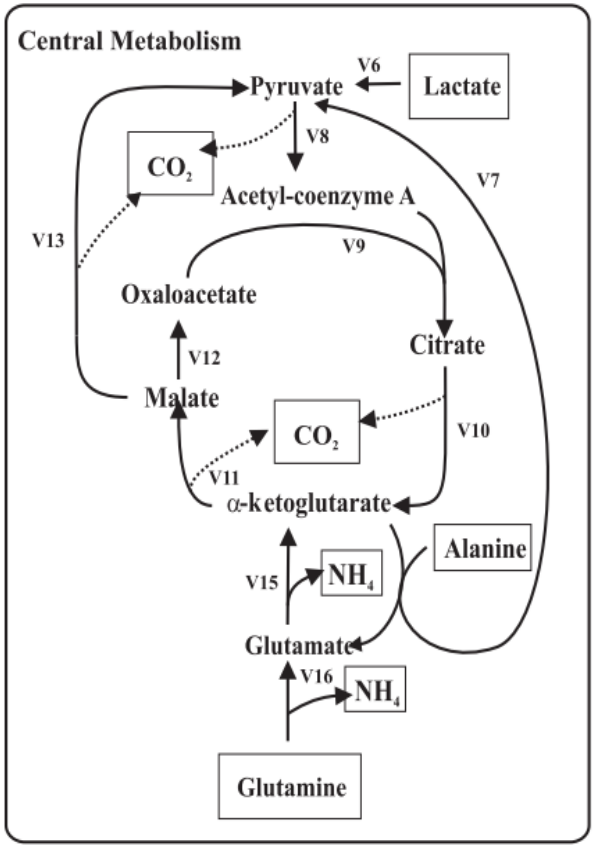
Metabolism is controlled by gene expression ..

but not only by that !

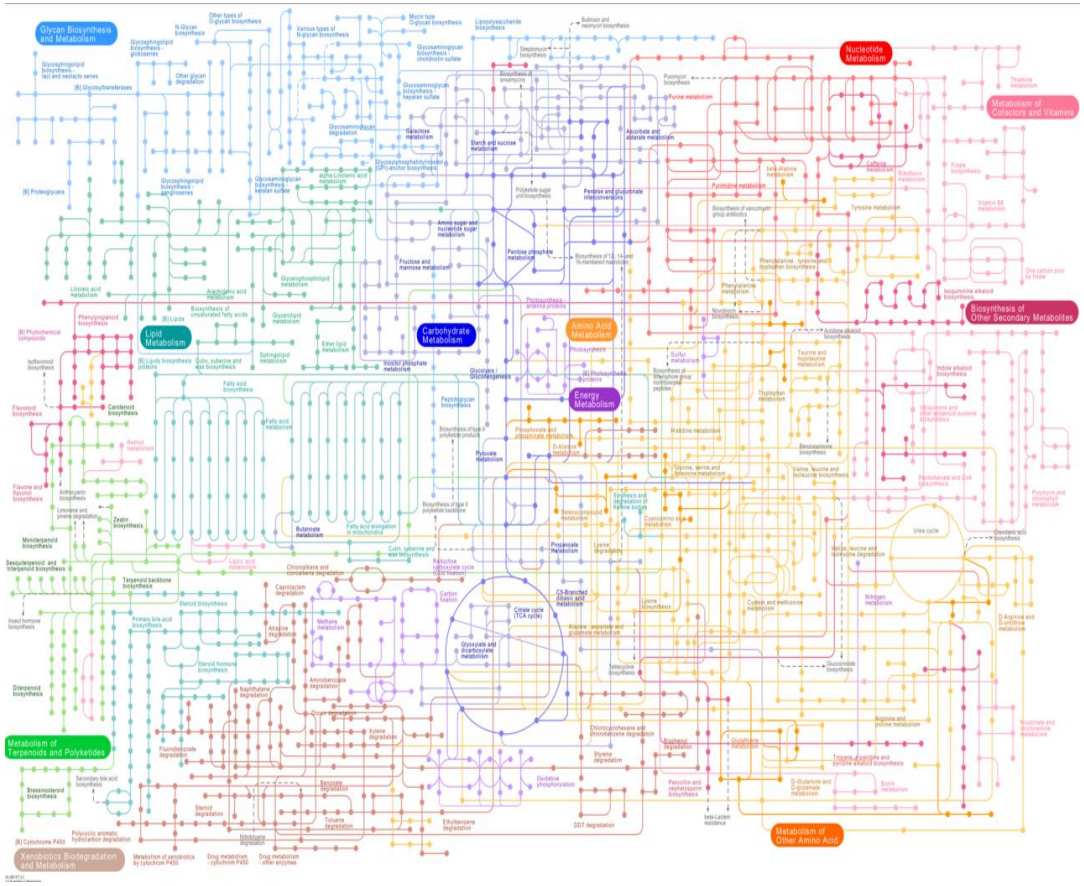
What is a metabolic network?

Metabolic network =

metabolites and metabolic reactions, forming a hypergraph



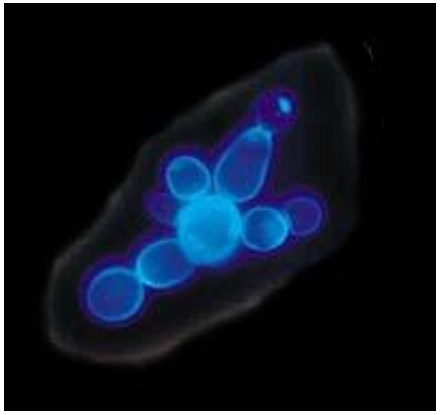
A few reactions in central metabolism

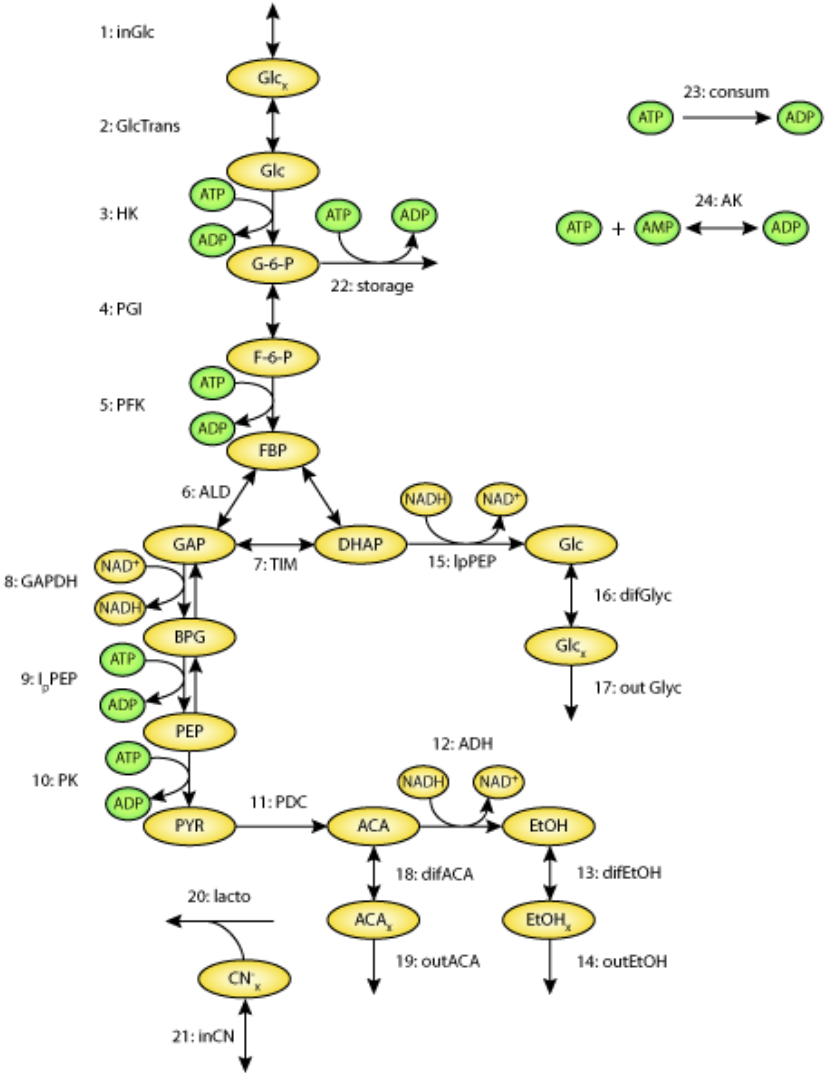


Overview of a genome-scale metabolic network (source: KEGG

How to model metabolism - with differential equation models!

How to simulate metabolic or signalling pathways?





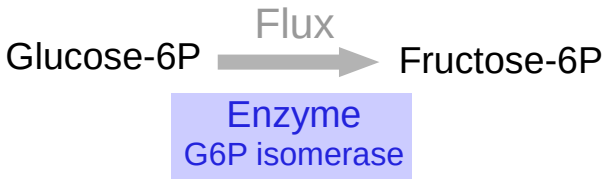
Biochemical entities: Metabolites, reactions, ...

Biochemical quantities: Concentrations, rates, …

Mathematical statements: Values, equations, ...

Full-scale model of glycolysis in Saccharomyces cerevisiae,
F. Hynne et al., 2001, Biophysical Chemistry (94), 121-163.

What we need to build a kinetic model: network structure and rate laws



Rate law

$$v = [\text{enzyme}] \frac{k_{\text{cat}} [\text{G6P}]}{[\text{G6P}] + K_{\text{M}}}$$

Main model types

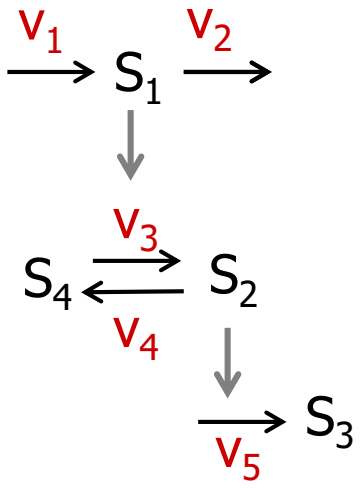
Kinetic models

- predict dynamics
- high data demand
- fully mechanistic

Constraint-based models

- predict stationary fluxes
- use network structure only
- use heuristic principles

From a network structure to a dynamical model



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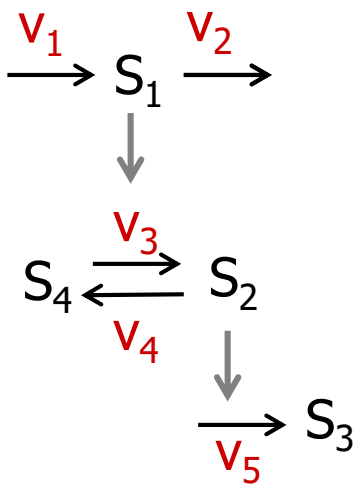

Metabolite Concentrations

Reaction rates

$$\vec{s} = \begin{pmatrix} S_1 \\ S_2 \\ S_3 \\ S_4 \end{pmatrix} \qquad \vec{v} = \begin{pmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \\ v_5 \end{pmatrix}$$

Differential equations

$d[S_1]/dt = v_1 - v_2$

$d[S_2]/dt = v_3 - v_4$

$d[S_3]/dt = v_5$

$d[S_4]/dt = -v_3 + v_4$

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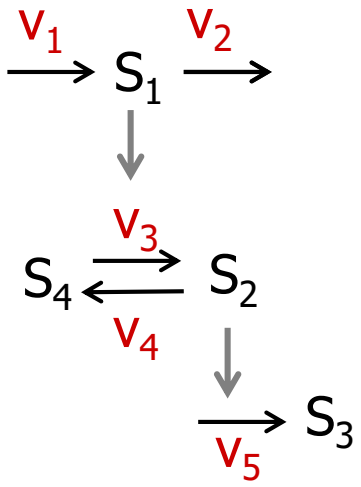

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$$\begin{pmatrix} 1 & -1 & 0 & 0 & 0 \\ 0 & 0 & 1 & -1 & 0 \\ 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & -1 & 1 & 0 \end{pmatrix} \times \begin{pmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \\ v_5 \end{pmatrix} = \begin{pmatrix} v_1 & -v_2 & +0 & +0 & +0 \\ 0 & +0 & +v_3 & -v_4 & +0 \\ 0 & +0 & +0 & +0 & v_5 \\ 0 & +0 & -v_3 & +v_4 & +0 \end{pmatrix}$$

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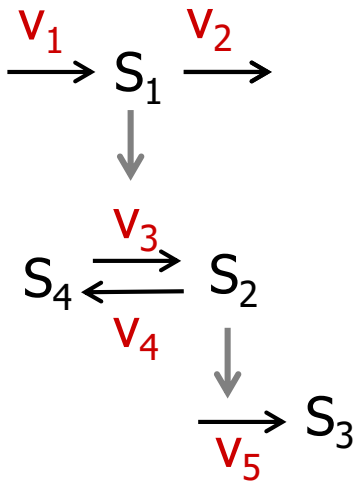


Metabolite Concentrations

$$\vec{s} = \begin{pmatrix} S_1 \\ S_2 \\ S_3 \\ S_4 \end{pmatrix}$$

Reaction rates

$$\vec{v} = \begin{pmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \\ v_5 \end{pmatrix}$$

Stoichiometric Matrix

$$\boldsymbol{N} = \begin{array}{c} \begin{matrix} v_1 & v_2 & v_3 & v_4 & v_5 \end{matrix} \\ \begin{pmatrix} 1 & -1 & 0 & 0 & 0 \\ 0 & 0 & 1 & -1 & 0 \\ 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & -1 & 1 & 0 \end{pmatrix} \end{array} \begin{matrix} S_1 \\ S_2 \\ S_3 \\ S_4 \end{matrix}$$

Differential equations

$d[S_1]/dt = v_1 - v_2$

$d[S_2]/dt = v_3 - v_4$

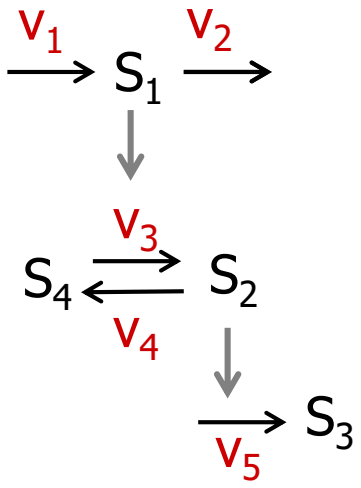
$d[S_3]/dt = v_5$

$d[S_4]/dt = -v_3 + v_4$

$$\begin{pmatrix} 1 & -1 & 0 & 0 & 0 \\ 0 & 0 & 1 & -1 & 0 \\ 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & -1 & 1 & 0 \end{pmatrix} \times \begin{pmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \\ v_5 \end{pmatrix} = \begin{pmatrix} v_1 & -v_2 & +0 & +0 & +0 \\ 0 & +0 & +v_3 & -v_4 & +0 \\ 0 & +0 & +0 & +0 & v_5 \\ 0 & +0 & -v_3 & +v_4 & +0 \end{pmatrix}$$

$$\boldsymbol{N} \times \vec{\boldsymbol{v}} = \boldsymbol{d[S]/dt}$$

From a network structure to a dynamical model



Matrix representation

$$\frac{\mathrm{d}\,\boldsymbol{S}}{\mathrm{d}\,t} = \mathbf{N}\boldsymbol{v}$$

$$N = \{n_{ij}\} \quad \begin{matrix} i = 1 \ldots n \\ j = 1 \ldots r \end{matrix}$$

$$S = (S_1, \ldots, S_n)^T$$

$$v = (v_1, \ldots, v_r)^T$$

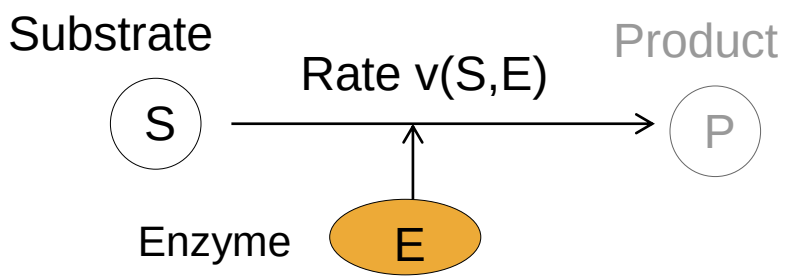
$$\frac{dS_i}{dt} = \sum_{j=1}^{r} n_{ij} v_j$$

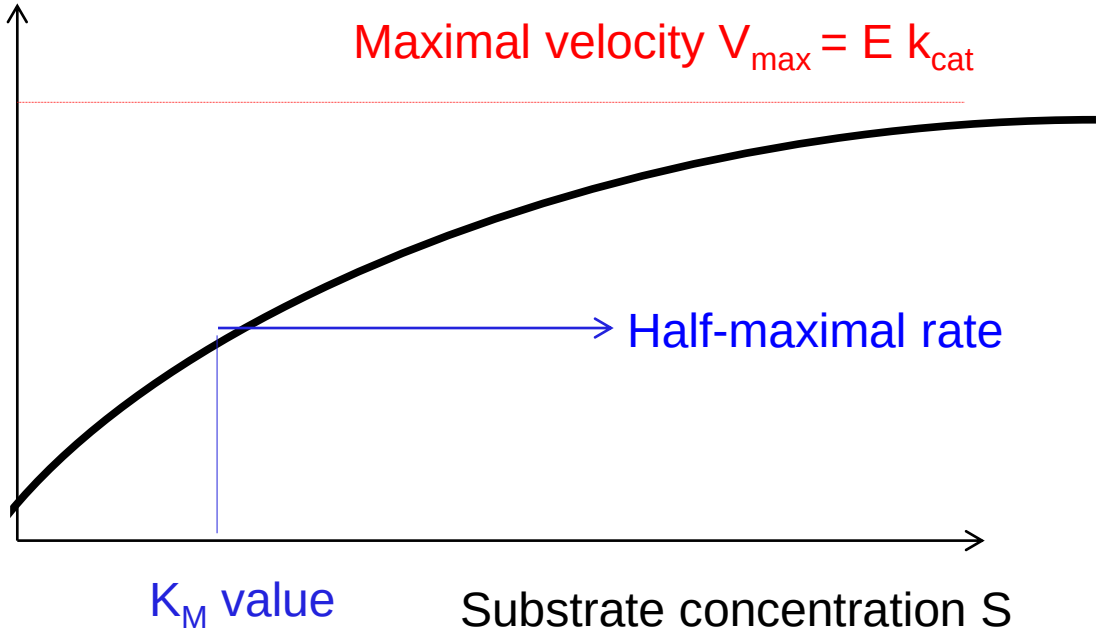
r – number of reactions
S_i – metabolite concentrations
v_j – reaction rates
n_{ij} – stoichiometric coefficients

Network properties

Individual reaction properties

A very popular rate law: meet the Michaelis-Menten kinetics!





Variables:

- Substrate concentration s
- Enzyme concentration E

Parameters:

- K_M value (in mM): inverse binding affinity
- Catalytic constant k_{cat} (in 1/s)
- Maximal number of conversions per time and enzyme molecule

Differential equations describe changes in every moment - integration yields the behaviour in time

External metabolite S_0:
we predefine its concentration!

Differential equations describe changes in every moment - integration yields the behaviour in time

A simple way to solve differential equations numerically (“Euler method”)

- Consider fixed, small time step!
- Start with initial values s(t=0)
- Use the updating rule:

$$s(t + \Delta t) = s(t) + \frac{ds}{dt} \Delta t$$

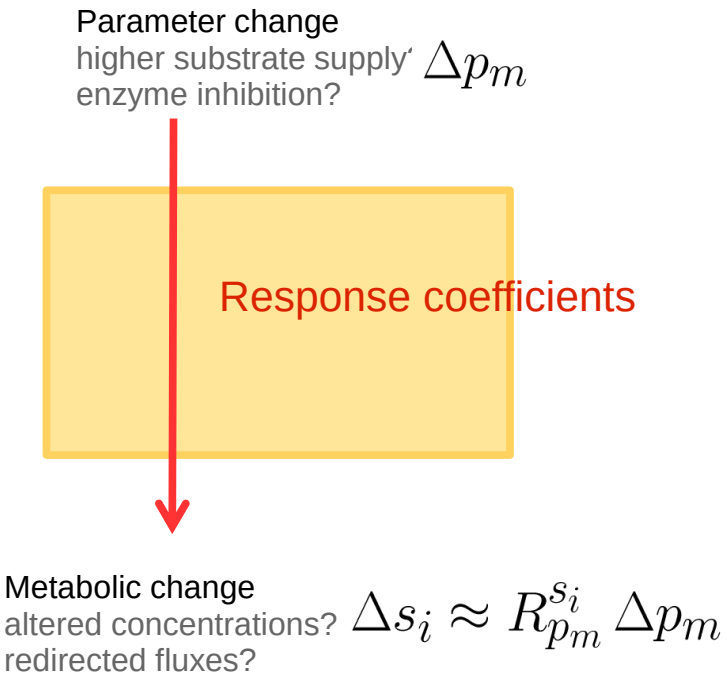
- Repeat the last step many times

Differential equations describe changes in every moment - integration yields the behaviour in time

Also see the video “Le système d’EDO” de DIGIT-BIO

Behaviour in time depends on small model details

Metabolic control analysis predicts global effects of small parameter perturbations



Metabolic control analysis predicts global effects of small parameter perturbations

Parameter change
higher substrate supply
enzyme inhibition?
Δp_m

Response coefficients

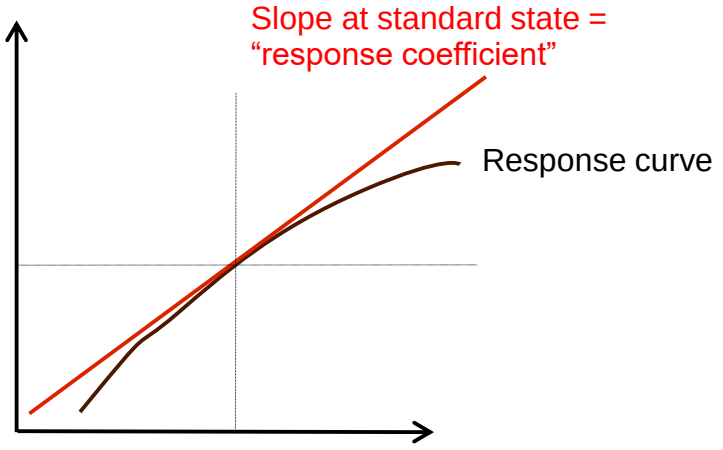
Metabolic change
altered concentrations?
redirected fluxes?
$\Delta s_i \approx R^{s_i}_{p_m} \Delta p_m$

1. Stationary concentrations *s*(*p*)

Solution of $0 = N\, v(s(p), p)$

2. Response coefficients

Systemic effect:
steady flux or concentration



Local cause:
e.g., single enzyme level

Kinetic models can predict cellular enzyme demands

Example model

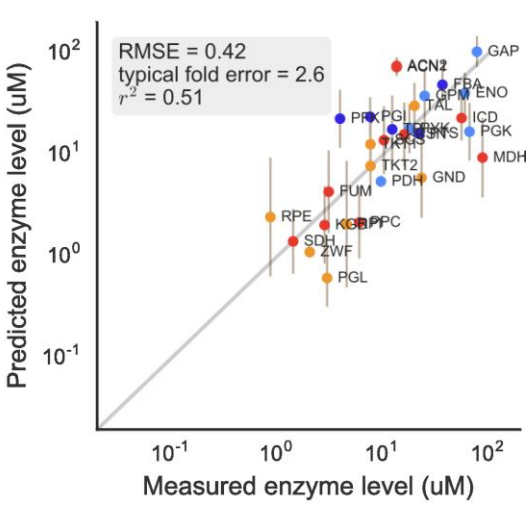
Enzymatic rate law

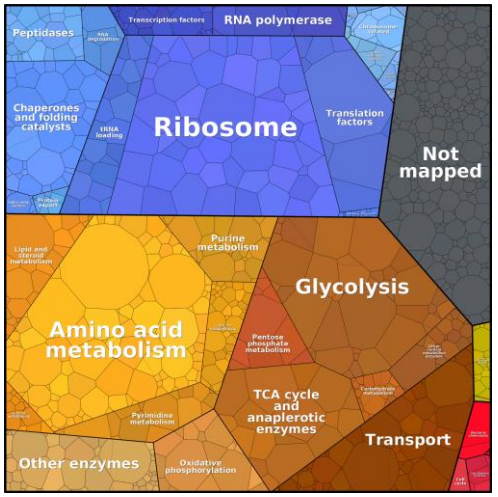
$$v = E\, f(a, b)$$

Enzyme cost function

$$\sum_l E_l = \sum_l \frac{v_l}{f_l(a, b)}$$

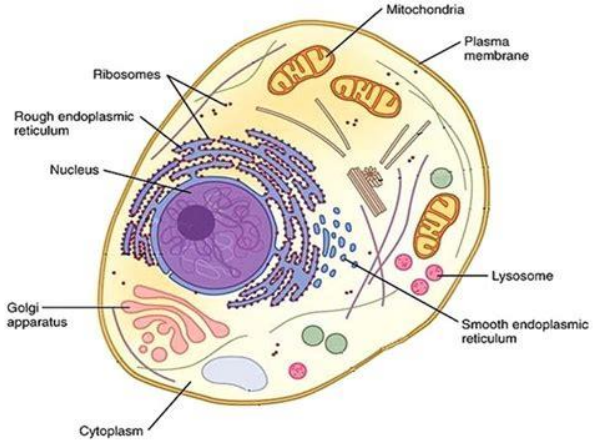
Enzyme predictions for *E. coli* central carbon metabolism



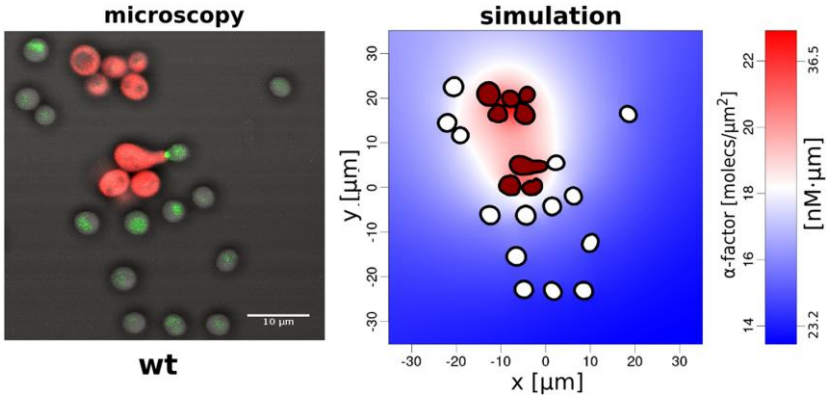


Noor et al. (2016), PLoS Comput Biol 12(10): e1005167

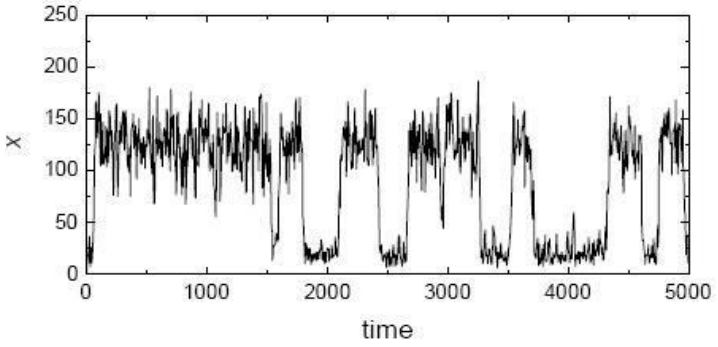
Kinetic models can be extended in many ways



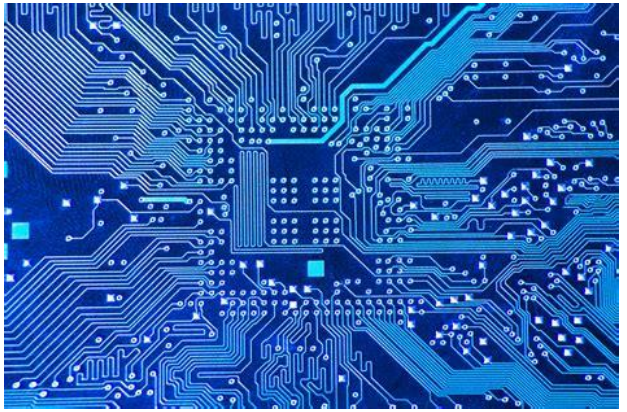
Models with cell compartments



Partial differential equations



Stochastic processes



Boolean models

Parameters

Kinetic models (ODE)

- 1 to 4 (or even more) parameters per reaction ➔ hundreds of parameters for models of central metablism
- Some values measured in vitro, many are not
- For large models, direct estimation by model fitting is unrealisticin; typically, insert known values, estimate (or guess) the others
- Ensemble models: sampling parameter values from random

Flux Balance Analysis

- At least 2 parameters + biomass equation for a whole network
- Determine experimentally using:
  - Biomass composition
  - Kinetics on substrates consumption
  - Kinetics on products excretion or fluxomics for some reactions
- Parameters estimation performed using linear regressions or directly from data (biomass equation)

Some possible applications

Kinetic models (ODE)

- Dynamic simulation of metabolic pathways (not really highly applied)
- Pharmacokinetics models (distribution of drugs in the body)
- Dynamic simulation of signaling pathways, cell cycle, gene expression, etc
- Metabolic steady states: sensitivity analysis ("Metabolic control analysis"), e.g. dependence of fluxes on enzyme levels
- Resource allocation models:

Flux Balance Analysis

- Predictions of phenotypes such as growth rate or metabolite excretion depending on the environmental conditions
- Predictions of fluxes of matter in different environmental conditions
- Predictions of essential genes and predictions of the effect of a inhibited/catalyzed reaction on the whole network
- Predictions of necessary network rewiring for desired phenotype
- Help to understand omics data such as transcriptomics, proteomics or Tnseq

Kinetic and constraint-based approaches can be coupled in different ways

One approach can provide parameters for the other one ..

- Kinetic models provide / explain parameters for FBA models (to relate fluxes to en
- FBA models provide flux distributions as a starting point for kinetic steady-state m

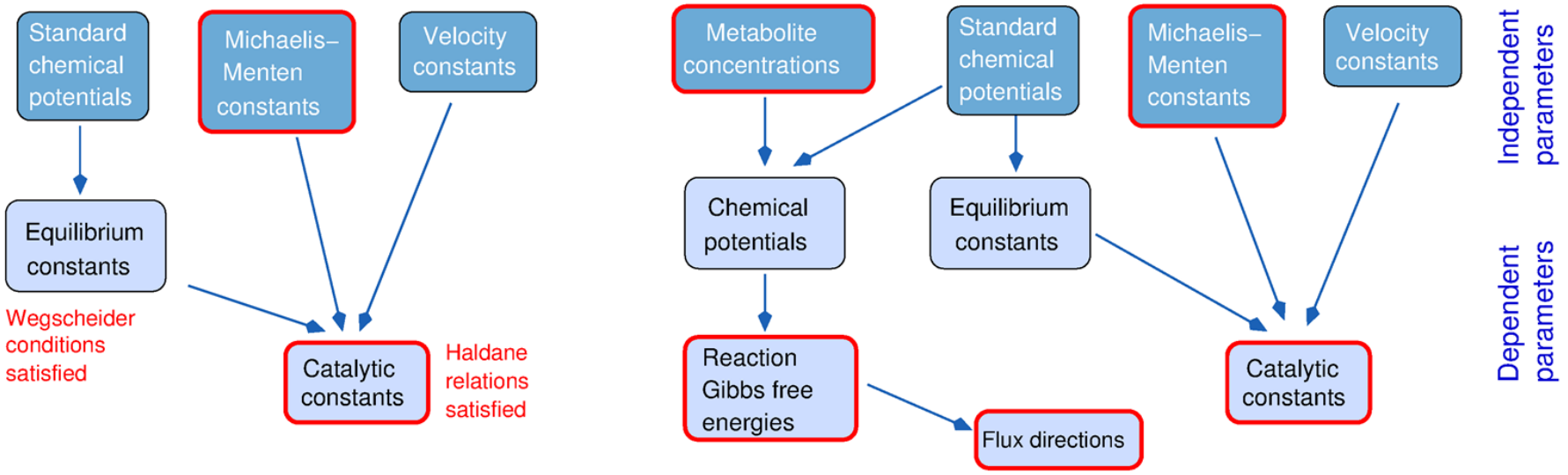
.. or they can actually be combined:

- “Hybrid model”: a large FBA model provides an “environment” (e.g. realistic bound
- “Dynamic FBA”: dynamic (ODE-like) simulation of a cell culture, where an FBA pr

Parameter balancing: a method for obtaining complete, consistent parameter sets for metabolic models

Problems:

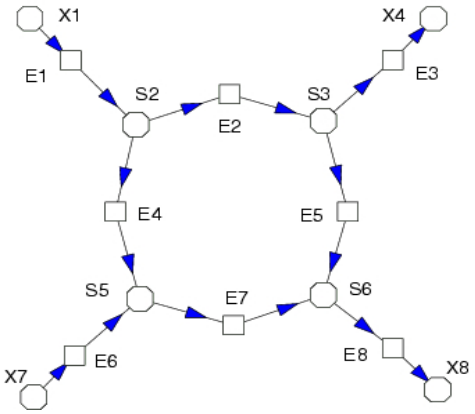
- Many model parameters are unknown or uncertain
- Some model parameters are physically and logically dependent
- Data values can contradict each other

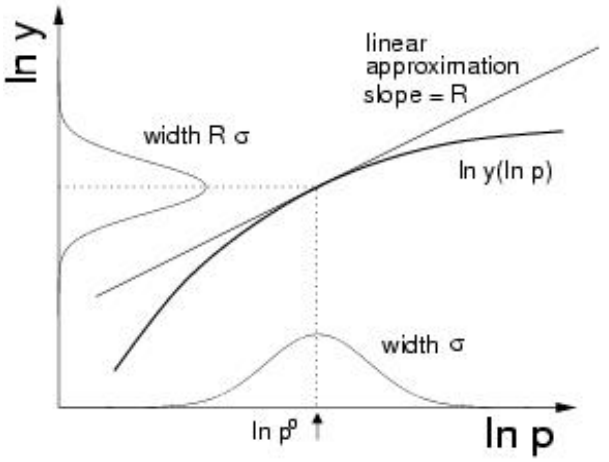


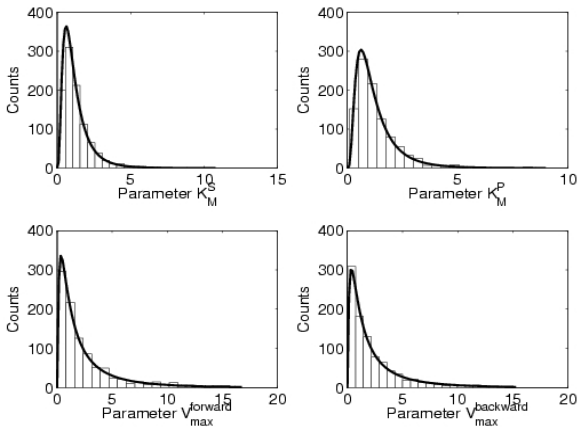
- Parameter balancing can be used for kinetic parameters and for
- thermodynamically feasible states (concentrations, Gibbs free energies etc)
- Parameter balancing can be run online (www.parameterbalancing.net)
- The workflow used data tables in SBtab format (www.sbtab.net)

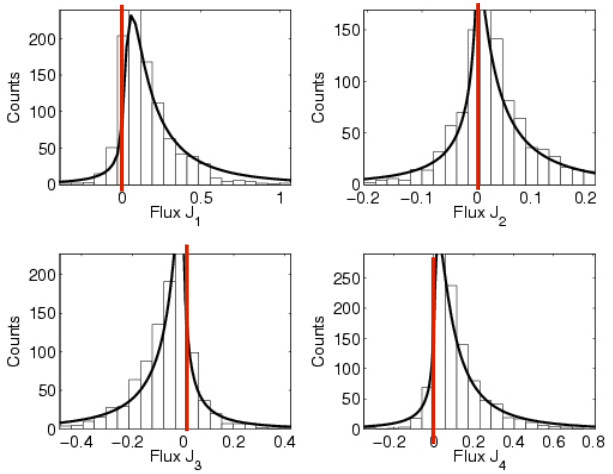
Lubitz T., Schulz M., Klipp E., Liebermeister W. (2010), Journal of Physical Chemistry B 114(49):16298-16303.

Variable and uncertain model parameters









Distribution of parameters

Distribution of reac

[Liebermeister W.](), [Klipp E.]() (2005), IEE Proc. Systems Biology, 152 (3), 97-107