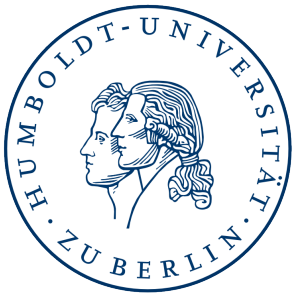
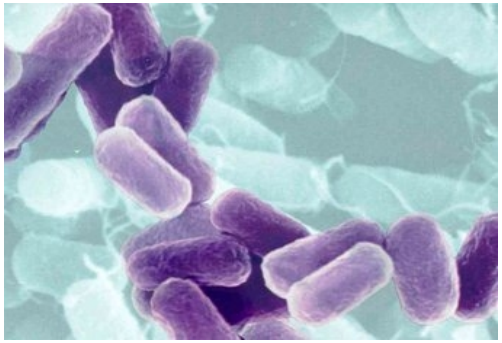


Metabolic networks

Wolfram Liebermeister

Humboldt-Universität zu Berlin – Theoretische Biophysik

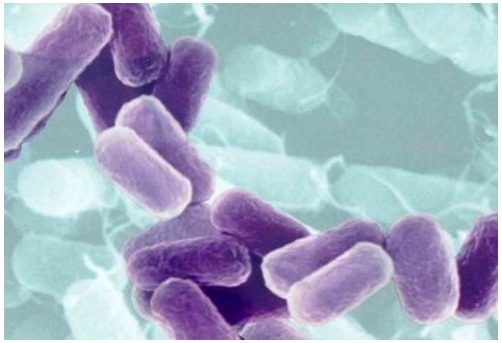
ASIM-Workshop
Trends in Computational Science and Engineering: Foundations of Modeling and Simulation



How can a living being emerge just from sugar, water, and a couple of salts?

Minimal Medium for *E. coli*

Glucose	5	g/l
Na_2HPO_4	6	g/l
KH_2PO_4	3	g/l
NH_4Cl	1	g/l
NaCl	0.5	g/l
$MgSO_4$	0.12	g/l
$CaCl_2$	0.01	g/l



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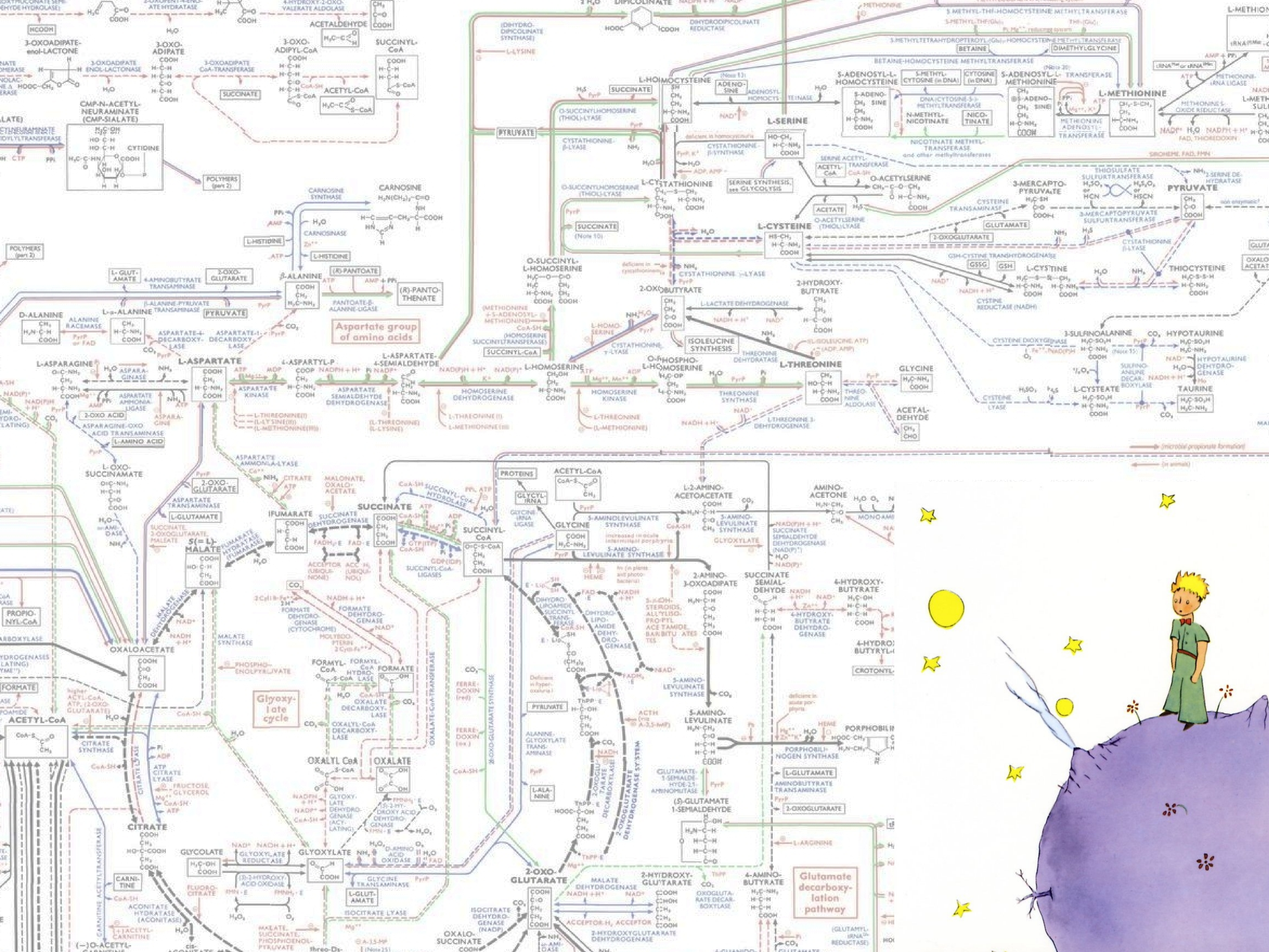
L'essentiel est invisible pour les yeux.


Aspartate group of amino acids
Glyoxylate cycle
Glutamate decarboxylation pathway
L-ASPARTATE
L-ASPARAGINE
β-ALANINE
CARNOSINE
L-HOMOCYSTEINE
L-METHIONINE
L-SERINE
L-CYSTATHIONINE
L-CYSTEINE
L-CYSTINE
PYRUVATE
L-HOMOSERINE
O-PHOSPHO-L-HOMOSERINE
L-THREONINE
GLYCINE
TAURINE
HYPOTAURINE
SUCCINATE
FUMARATE
S(–)-MALATE
OXALOACETATE
ACETYL-CoA
CITRATE
GLYOXYLATE
GLYCOLATE
FORMATE
OXALATE
SUCCINYL-CoA
2-OXO-GLUTARATE
5-AMINO-LEVULINATE
PORPHOBILINOGEN
4-AMINO-BUTYRATE
SUCCINATE SEMIALDEHYDE
4-HYDROXY-BUTYRATE

Metabolic networks produce materials and energy for the cell

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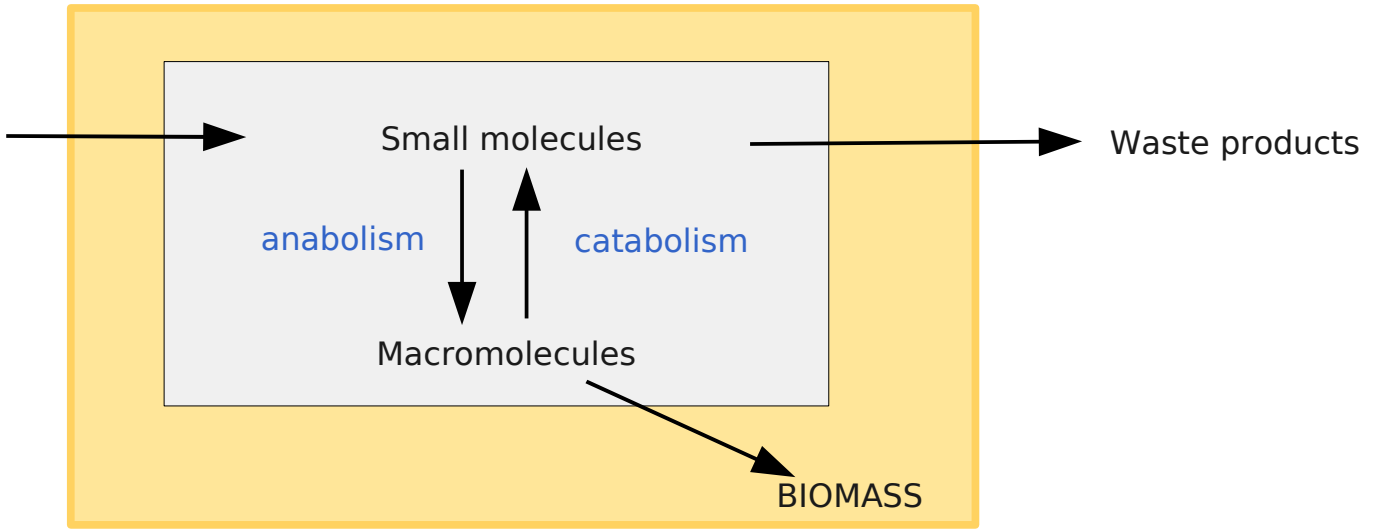
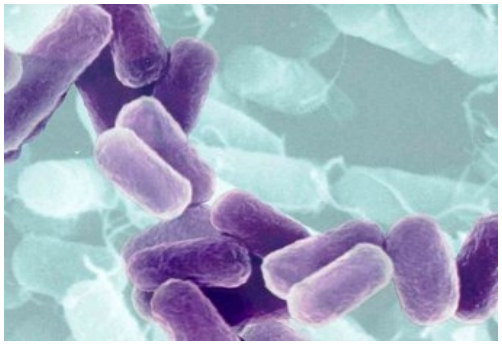




Overview

What are metabolic networks and how do they work ?

How can we use models to understand their dynamics ?

How can we predict fluxes in large networks ?

How do metabolic systems respond to perturbations ?

What standards, resources, and software are available ?

Metabolic networks

Genome-scale network models of *E. coli* metabolism

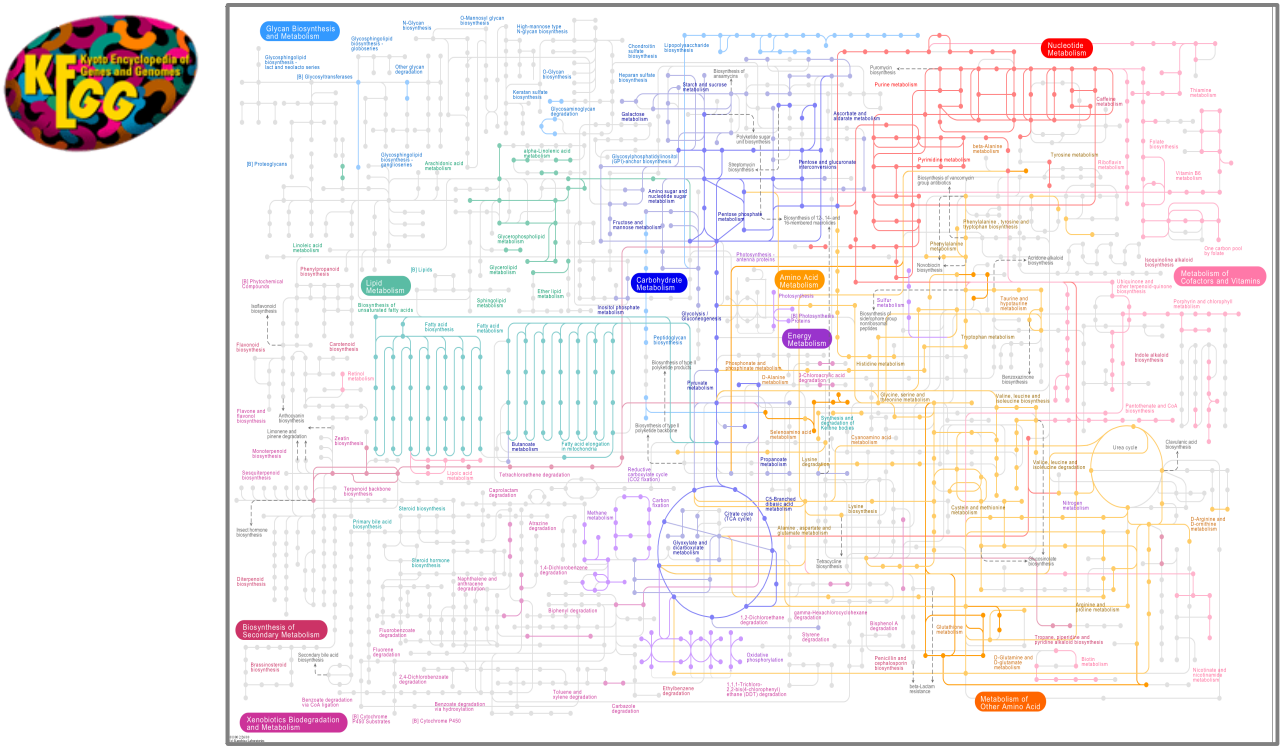
Molecular Systems Biology 3; Article number 121; doi:10.1038/msb4100155
Citation: ***Molecular Systems Biology*** **3:121**

www.molecularsystemsbiology.com

molecular systems biology

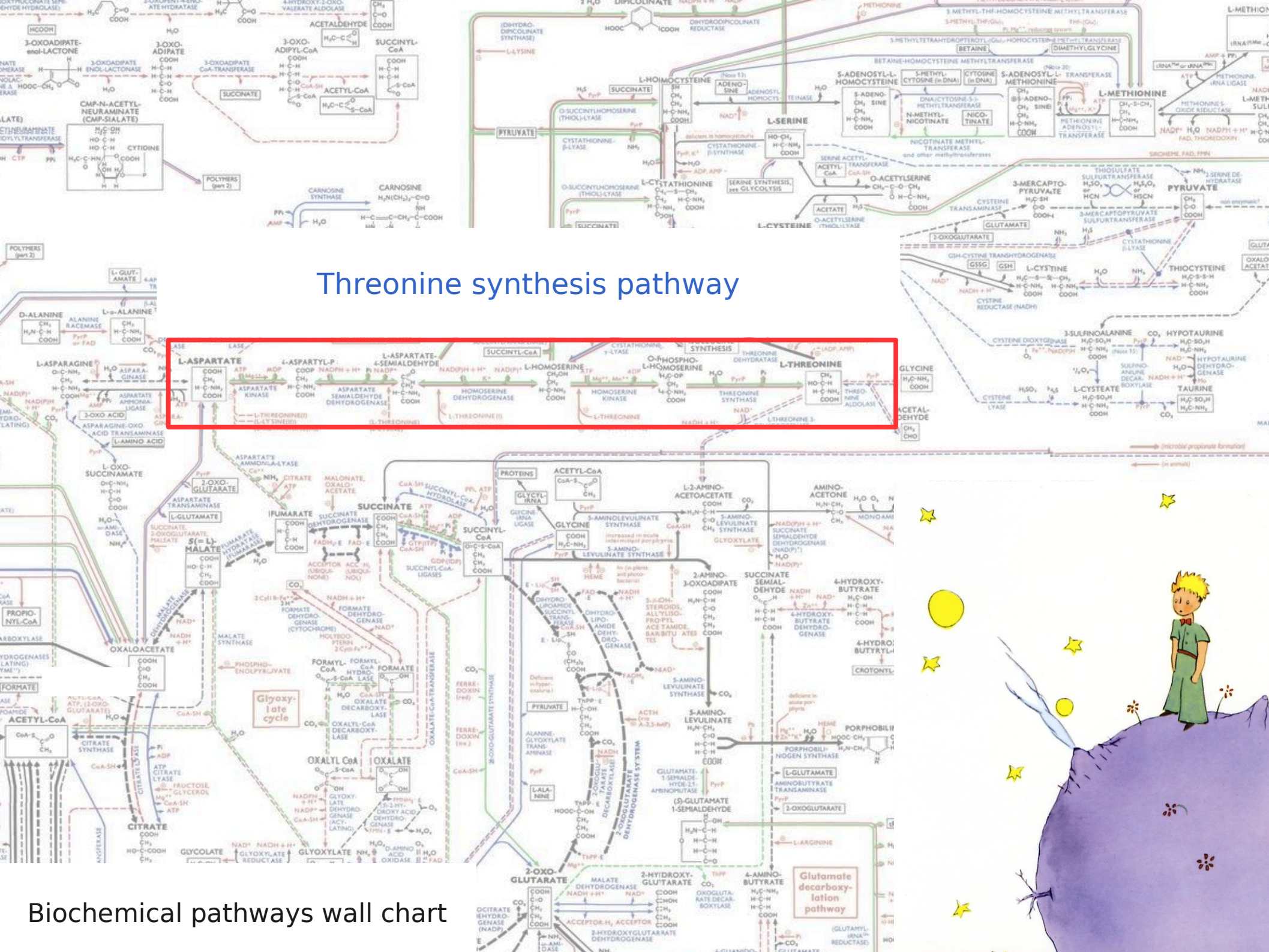
A genome-scale metabolic reconstruction for *Escherichia coli* K-12 MG1655 that accounts for 1260 ORFs and thermodynamic information

Adam M Feist[1], Christopher S Henry[2], Jennifer L Reed[1], Markus Krummenacker[3], Andrew R Joyce[1], Peter D Karp[3], Linda J Broadbelt[2], Vassily Hatzimanikatis[4] and Bernhard Ø Palsson[1,*]



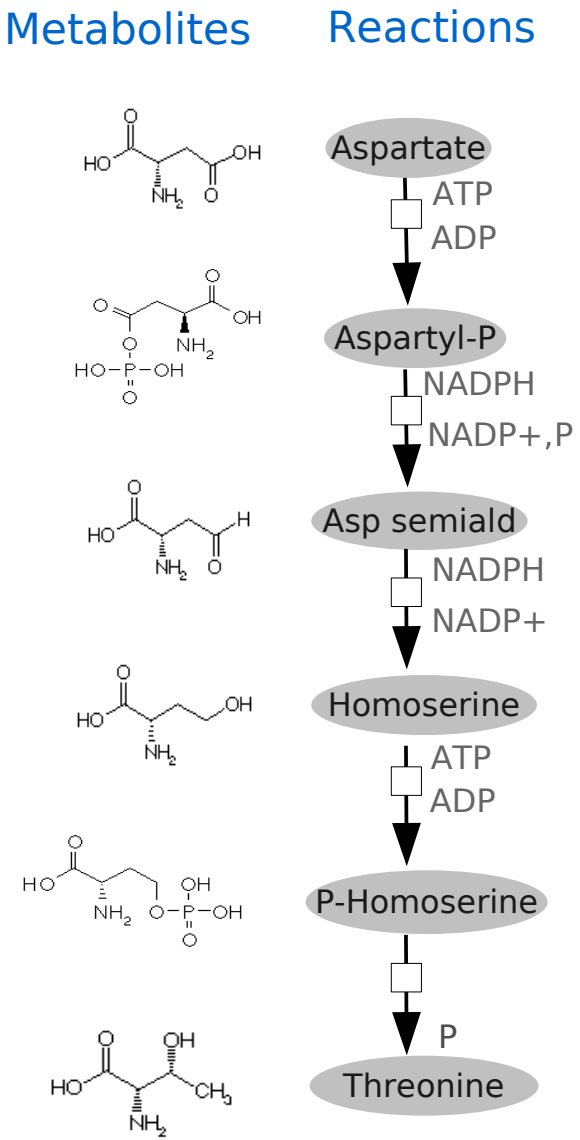
http://www.genome.jp/kegg/pathway/map/map01100.html

Threonine synthesis pathway



Biochemical pathways wall chart

Metabolic networks have several levels of regulation



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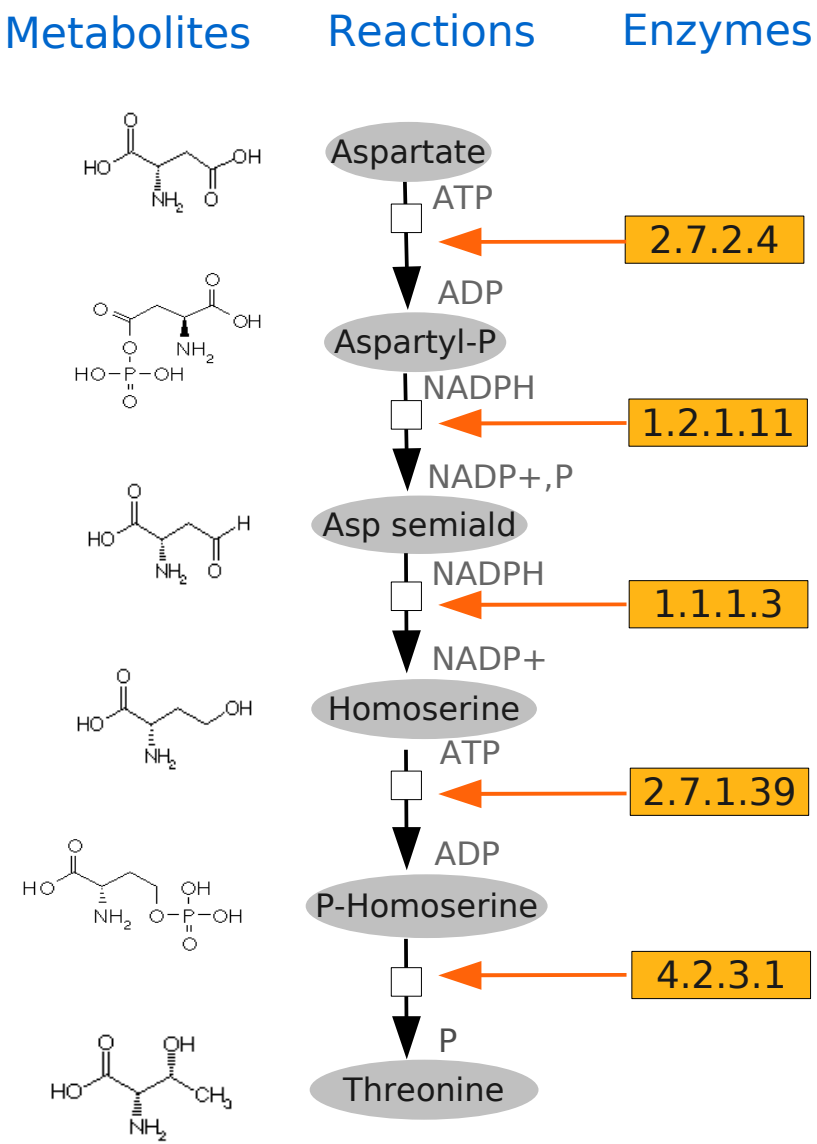

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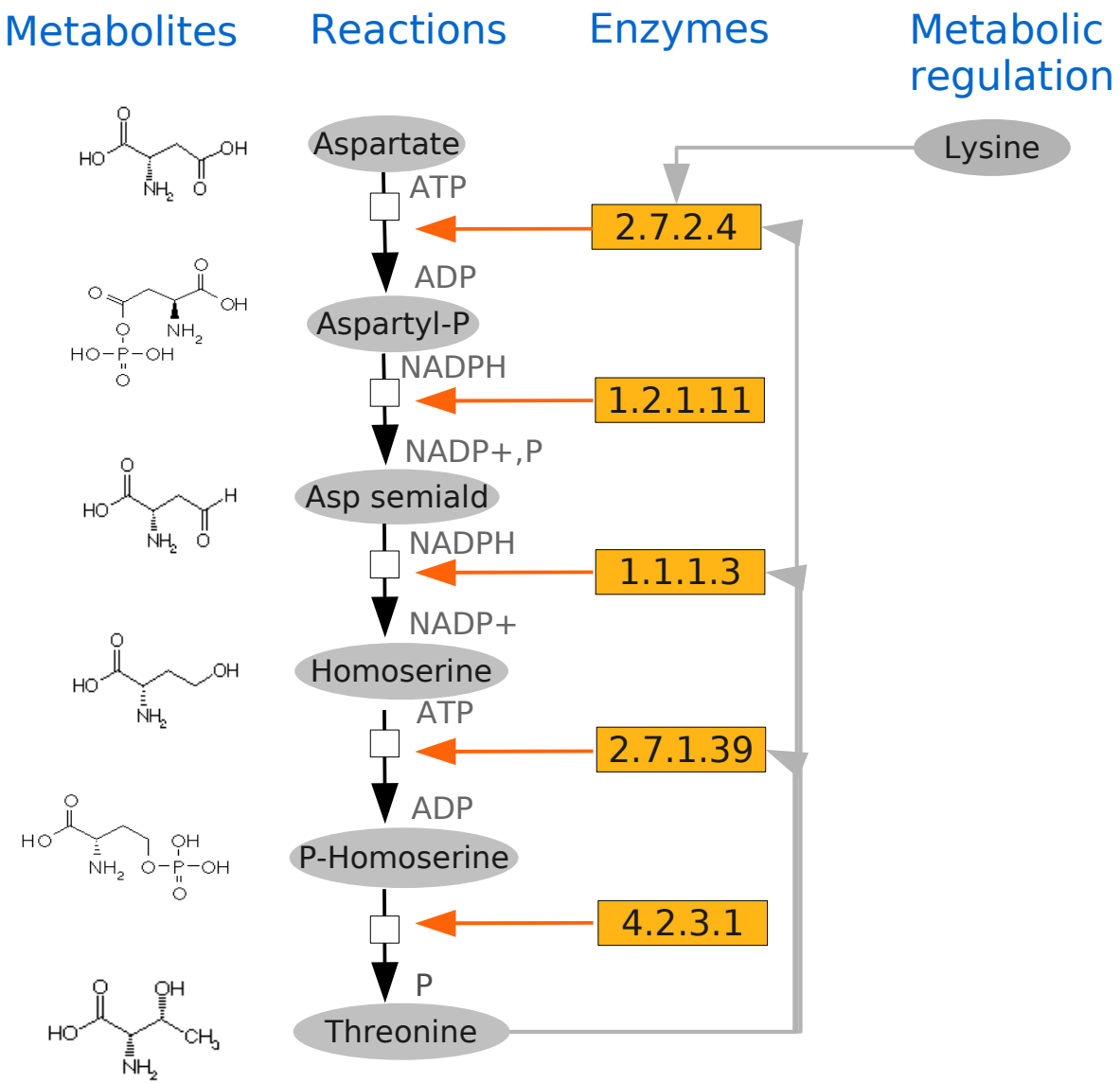

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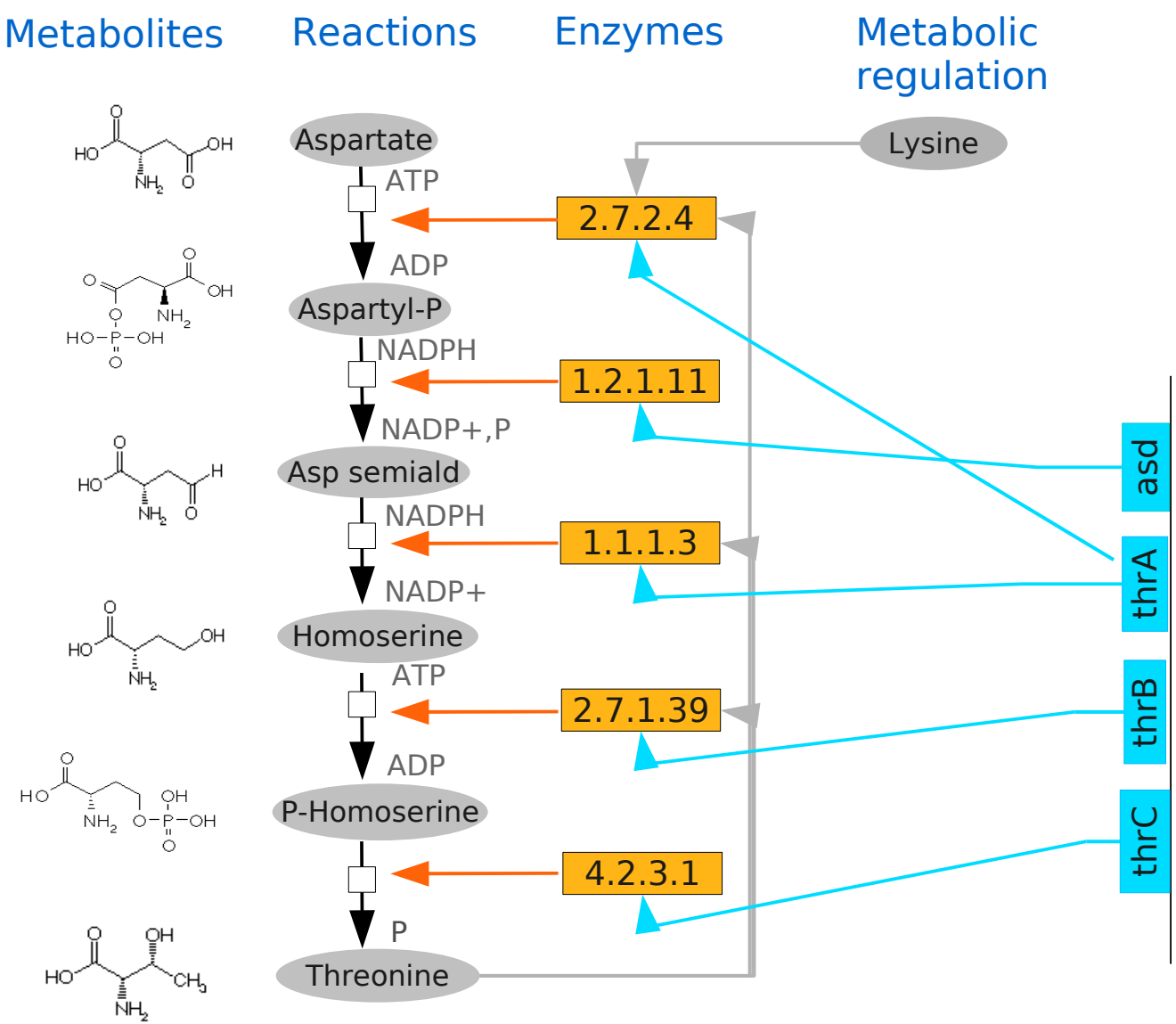

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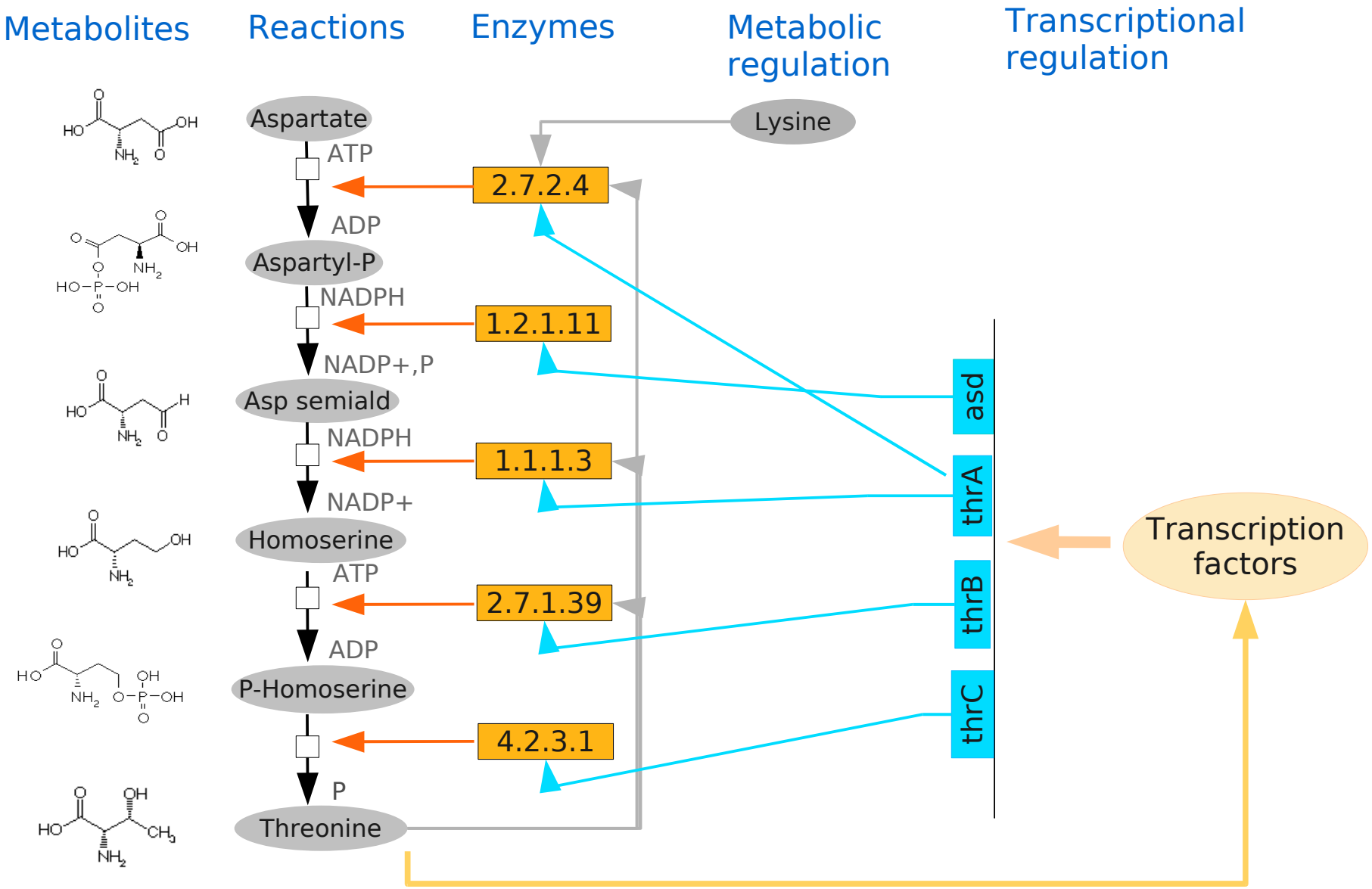
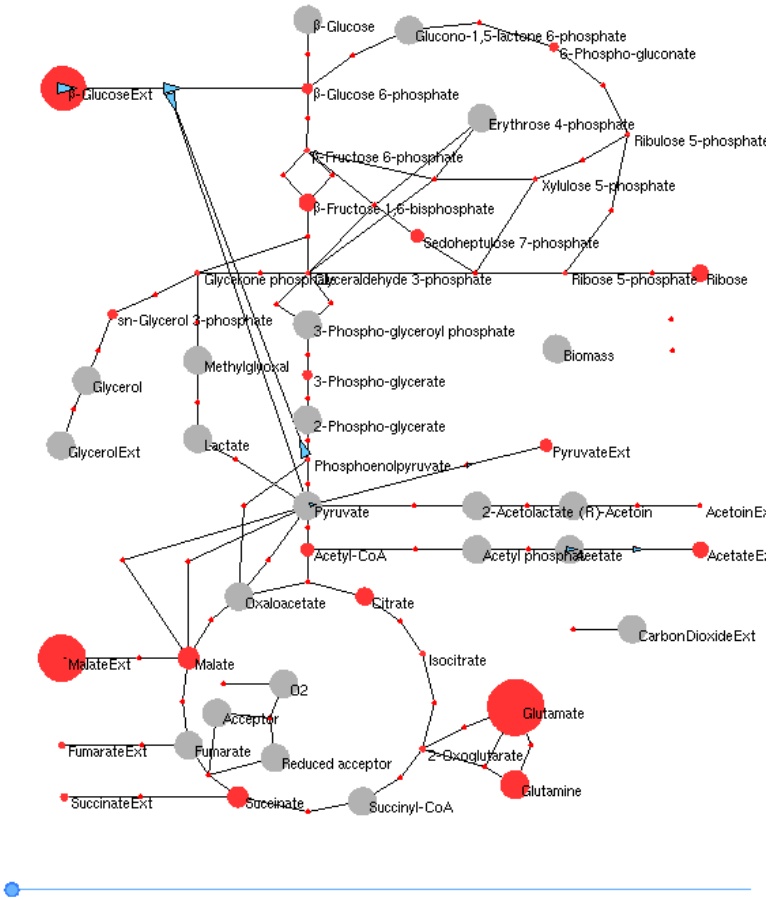


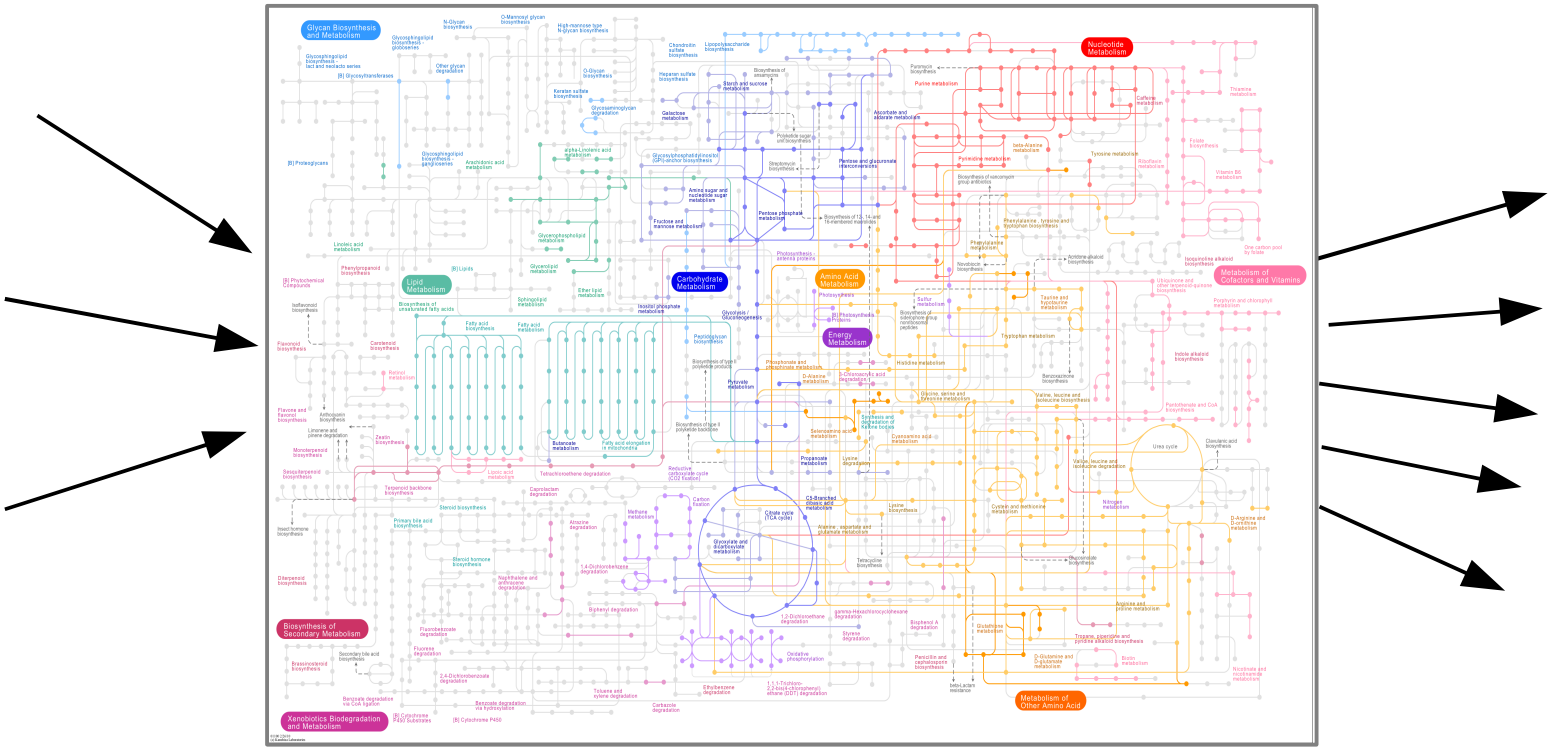
Multi-omics data show metabolism as a dynamic system



Measured uptake rates and concentrations
in *B. subtilis* central metabolism
after adding malate to a glucose medium.

Kinetic models

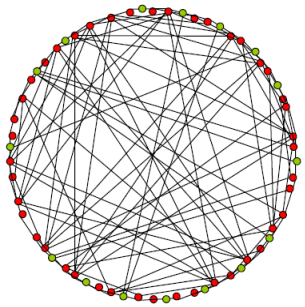
How do metabolic networks work?



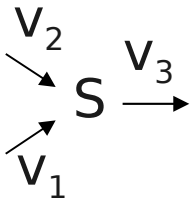
- What compounds can the cell produce?
- On which nutrient media can the cell survive?
- What do the metabolic fluxes look like ?
- How do they respond to varying conditions?
- How is all this regulated?
- What conclusions can we draw from limited data?

Modelling approaches for different complexity

Topological Analysis



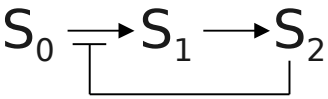
Flux Balance Analysis



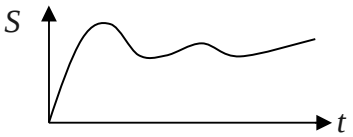
$$\frac{d\,\boldsymbol{S}}{dt} = \boldsymbol{N}\cdot\boldsymbol{v} = \boldsymbol{0}$$

$$v_1 + v_2 = v_3$$

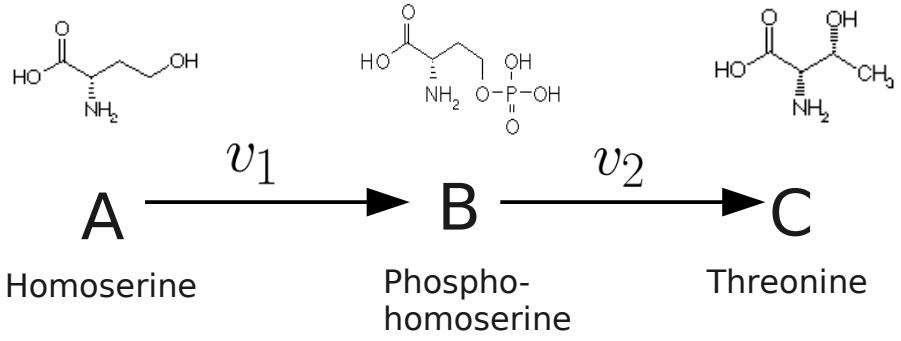
Kinetic modeling



$$\frac{d\,\boldsymbol{S}}{dt} = \boldsymbol{N}\cdot\boldsymbol{v}\left(\boldsymbol{S},\boldsymbol{p}\right)$$



Kinetic models describe the dynamics of biochemical reactions



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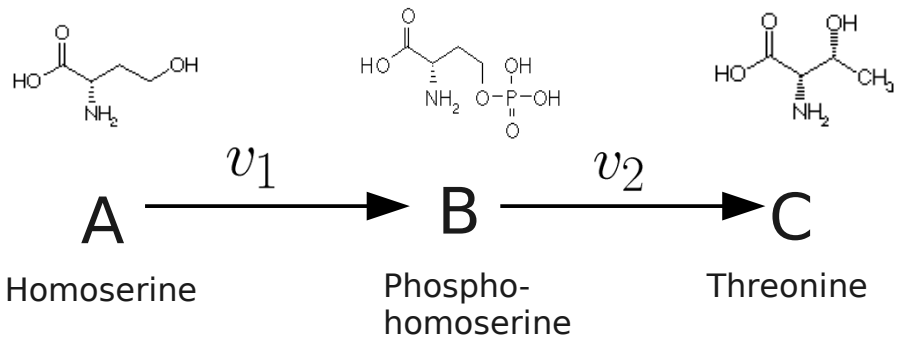


Reaction rate (“kinetic equations”)

How often does the reaction occur per time ?

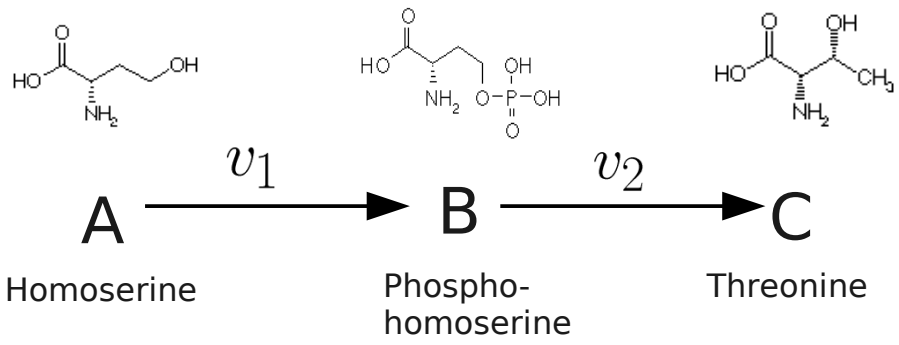
$$v = k_+ a - k_- b$$

reaction rate

kinetic constant

concentration

Kinetic models describe the dynamics of biochemical reactions



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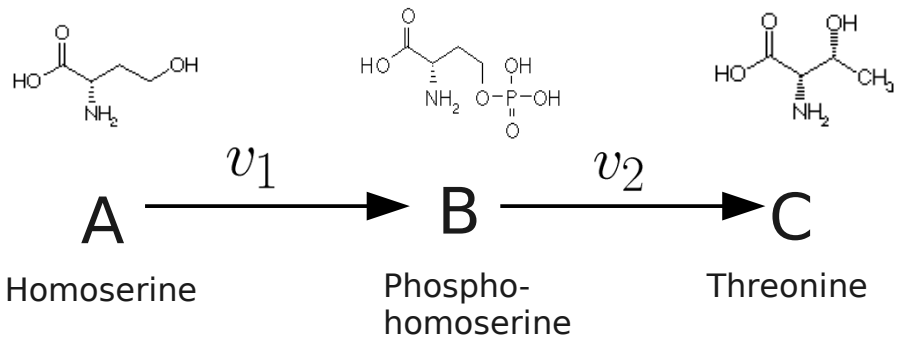
reaction rate — kinetic constant — concentration

System equations

How do the concentrations change over time?

$$\begin{aligned} \mathrm{d}a/\mathrm{d}t &= -v_1 \\ \mathrm{d}b/\mathrm{d}t &= v_1 - v_2 \\ \mathrm{d}c/\mathrm{d}t &= v_2 \end{aligned}$$

Kinetic models describe the dynamics of biochemical reactions



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concentration change

stoichiometric coefficient

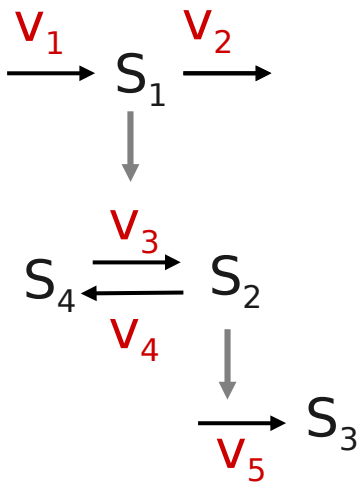
kinetic law for reaction velocity

$$\frac{\mathrm{d}x_i}{\mathrm{d}t} = \sum_l n_{il}\, v_l(x, p)$$

concentrations

kinetic parameters and enzyme concentrations

System equations – an example



Metabolite Concentrations

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

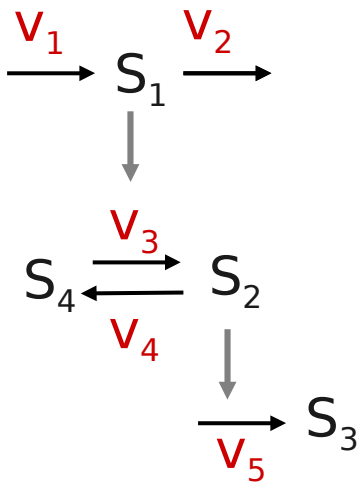
Reaction rates

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

Stoichiometric Matrix

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

System equations – an example



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ODEs

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

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

$d[S_3]/dt = v_5$

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

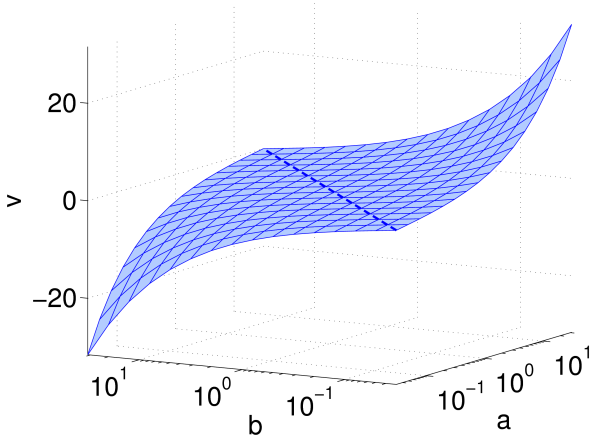
$$\begin{pmatrix} 1 & -1 & 0 & 0 & 0 \\ 0 & 0 & 1 & -1 & 0 \\ 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & -1 & 1 & 0 \end{pmatrix} \times \begin{pmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \\ v_5 \end{pmatrix} = \begin{pmatrix} v_1 & -v_2 & +0 & +0 & +0 \\ 0 & +0 & +v_3 & -v_4 & +0 \\ 0 & +0 & +0 & +0 & v_5 \\ 0 & +0 & -v_3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

$$\boldsymbol{N} \quad \mathbf{x} \quad \vec{\boldsymbol{v}} \quad = \quad \vec{\boldsymbol{d[S]/dt}}$$

The big problem in kinetic modelling: each enzyme is different !!

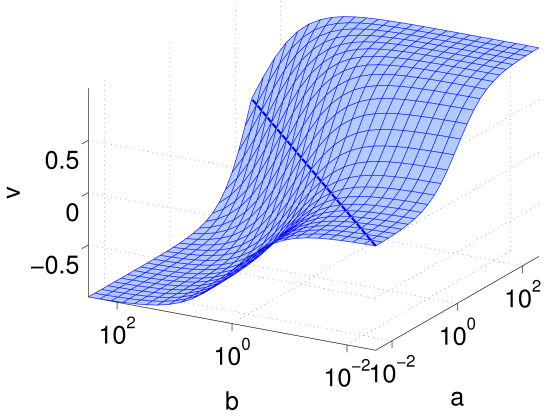
Mass-action kinetics (non-enzymatic reactions)

$$v = k_+ a - k_- b$$



Michaelis-Menten kinetics (simple enzymatic law)

$$v = \frac{v_+^{\max}(a/k_{\mathrm{A}}^{\mathrm{M}}) - v_-^{\max}(b/k_{\mathrm{B}}^{\mathrm{M}})}{1 + (a/k_{\mathrm{A}}^{\mathrm{M}}) + (b/k_{\mathrm{B}}^{\mathrm{M}})}$$



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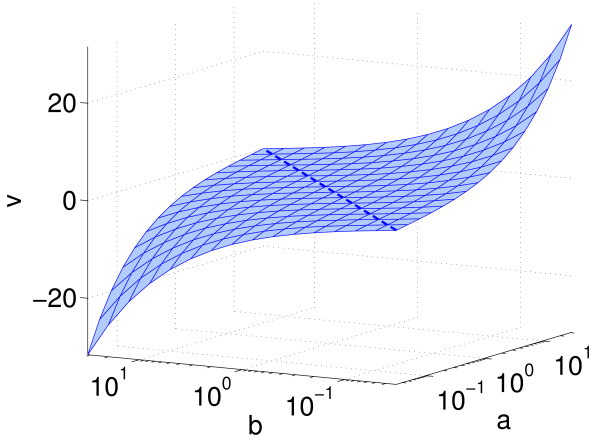

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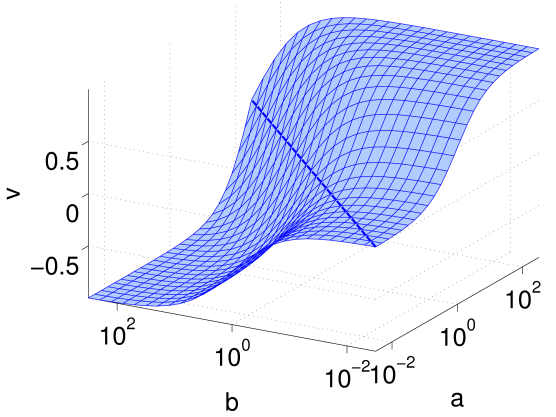


Thermodynamics helps to reduce unknown parameters

Chemical equilibrium

$$0 = v(a^{\mathrm{eq}}, b^{\mathrm{eq}}) = v_+^{\max}\frac{a^{\mathrm{eq}}}{k_A^M} - v_-^{\max}\frac{b^{\mathrm{eq}}}{k_B^M}$$

Haldane relation

$$k^{\mathrm{eq}} = \frac{b^{\mathrm{eq}}}{a^{\mathrm{eq}}} = \frac{v_+^{\max} k_B^M}{v_-^{\max} k_A^M}$$

Constraint-based models predict metabolic fluxes in large networks

External metabolites (e.g. extracellular or buffered)
Treated as fixed parameters

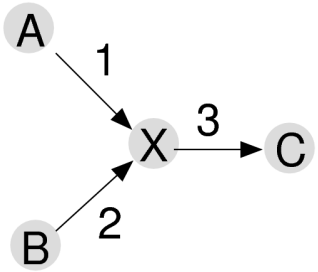
Intracellular metabolites (dynamic)
Concentration changes due to chemical reactions

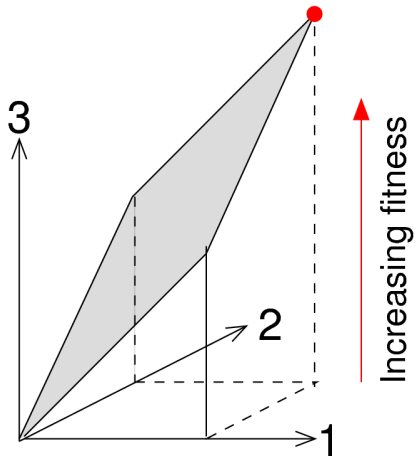
Stationary (=steady) state
A state in which all variables remain constant in time

Stationarity condition in kinetic models

$$\frac{\mathrm{d}c}{\mathrm{d}t} = N v = 0$$

Condition on the flux vector
Kinetic rate laws do not play a role!





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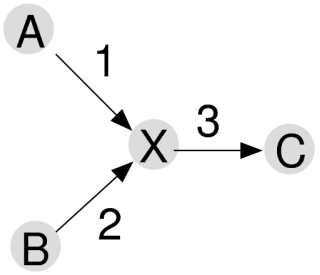
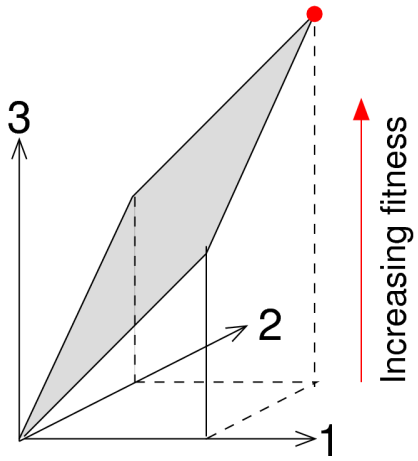




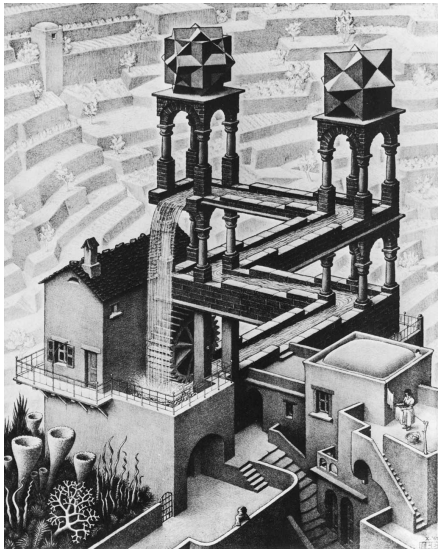
Flux balance analysis
predicts flux distributions for large networks

Stationarity + Upper and lower bounds on fluxes
→ Convex set in flux space

Linear optimisation (e.g. maximal product yield)
→ Linear programming problem

Fluxes have to satisfy thermodynamic constraints

1. Wegscheider conditions



$$f = -\nabla\Phi \quad \Rightarrow \quad \oint f(s)\cdot \mathrm{d}s = 0$$

$$\Delta x = N^{\mathrm{T}} x \quad \Rightarrow \quad K^{\mathrm{T}}\Delta x = 0 \quad (\text{where } NK = 0)$$

Equilibrium constants	$K^{\mathrm{T}} \ln k^{\mathrm{eq}} = 0$
Mass-action ratios	$K^{\mathrm{T}} \ln q^{\mathrm{ma}} = 0$
Reaction affinities	$K^{\mathrm{T}} A = -K^{\mathrm{T}} \Delta\mu = 0$

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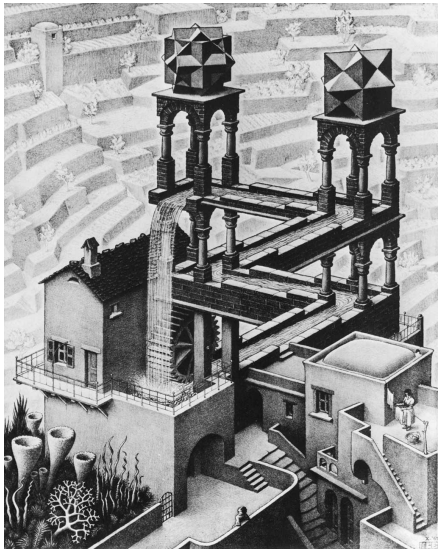

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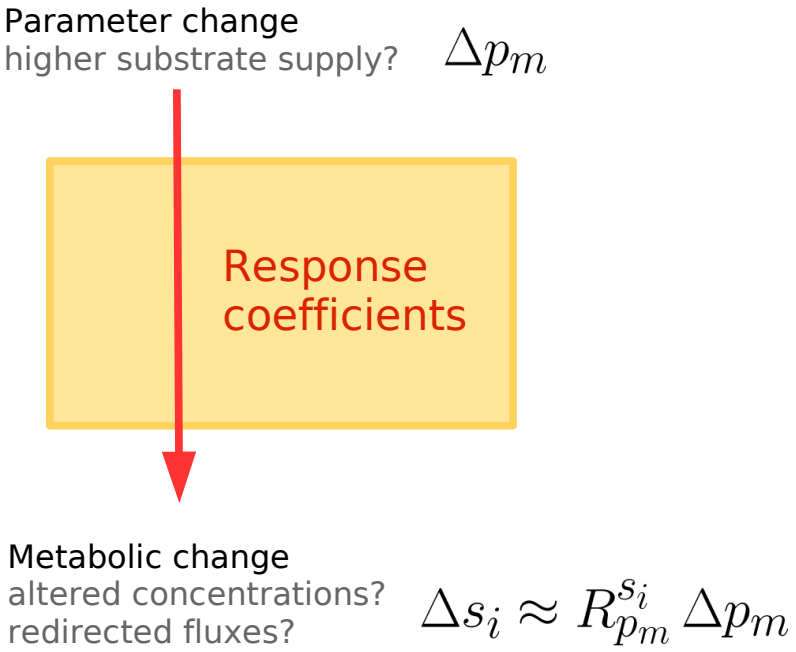
2. Flux directions and affinities (positive entropy production !)

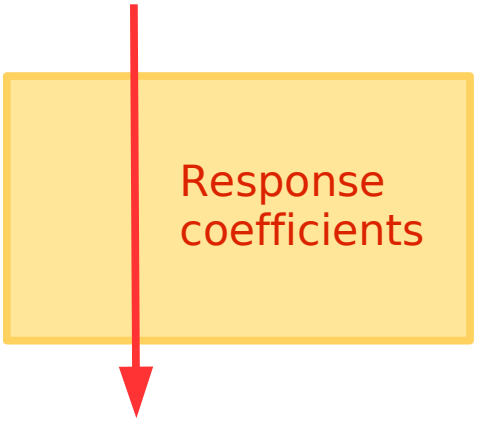
$$v_r \neq 0 \quad \Rightarrow \quad \mathrm{sign}(v_r) = \mathrm{sign}(A_r) = -\mathrm{sign}(\Delta\mu_r)$$

Metabolic control analysis traces the global effects of local changes



Metabolic control analysis traces the global effects of local changes

Parameter change
higher substrate supply? Δp_m

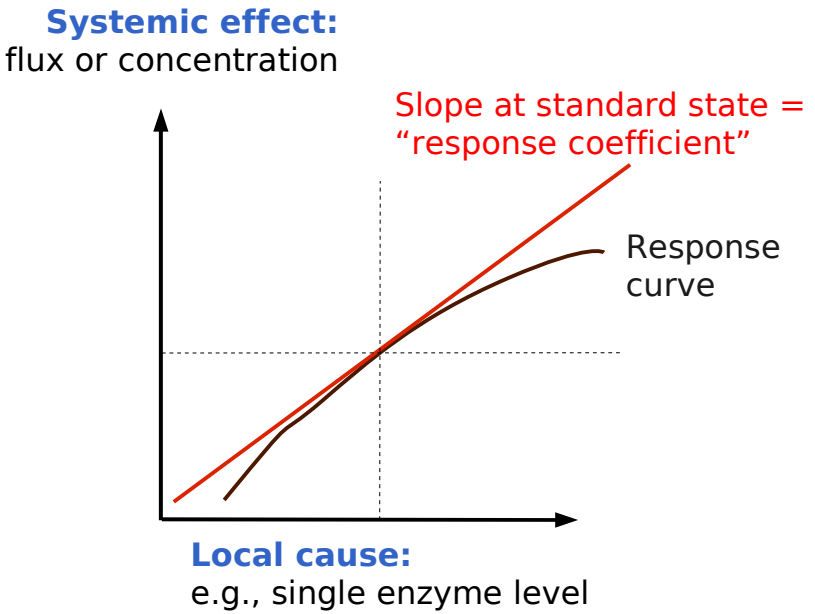


Metabolic change
altered concentrations?
redirected fluxes? $\Delta s_i \approx R^{s_i}_{p_m} \Delta p_m$

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

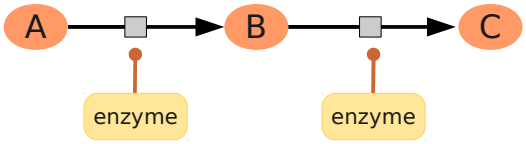
Solution of $0 = N\, v(s(p), p)$

2. Response coefficients



Summary: Modelling formalisms for biochemical systems

Kinetic models



concentration

stoichiometry

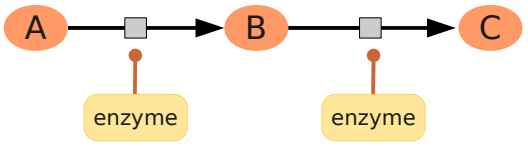
reaction rate

$$\frac{\mathrm{d}x_i}{\mathrm{d}t} = \sum_l n_{il}\, v_l(x,p)$$

parameters

Summary: Modelling formalisms for biochemical systems

Kinetic models



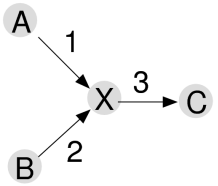
concentration — stoichiometry — reaction rate

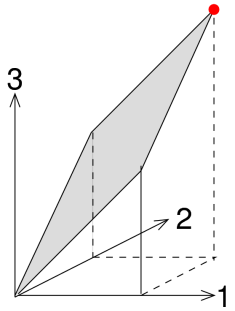
$$\frac{\mathrm{d}x_i}{\mathrm{d}t} = \sum_l n_{il}\, v_l(x,p)$$

parameters

Constraint-based models (e.g., flux balance analysis)

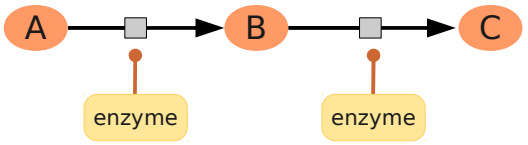
$$\frac{\mathrm{d}x}{\mathrm{d}t} = 0 \quad \Rightarrow \quad N\,v = 0$$

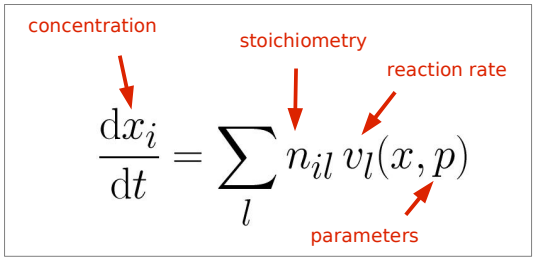




Summary: Modelling formalisms for biochemical systems

Kinetic models





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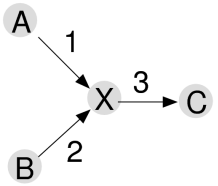
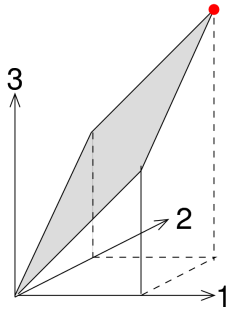
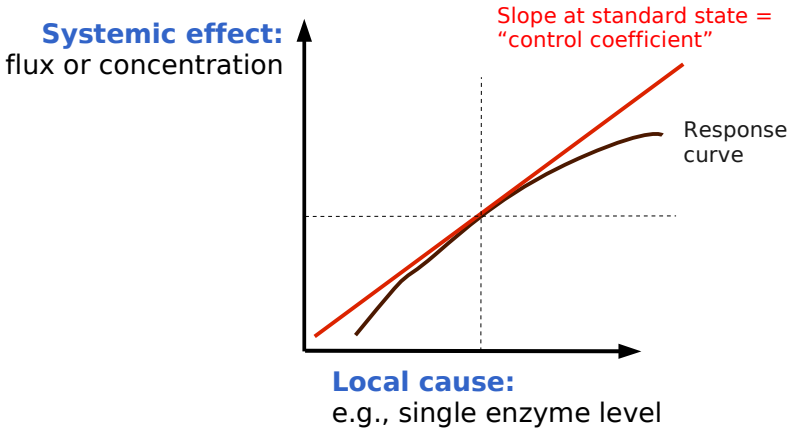


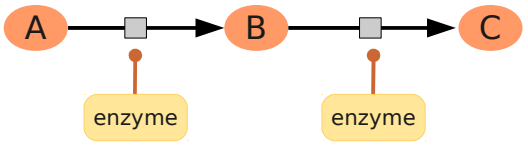


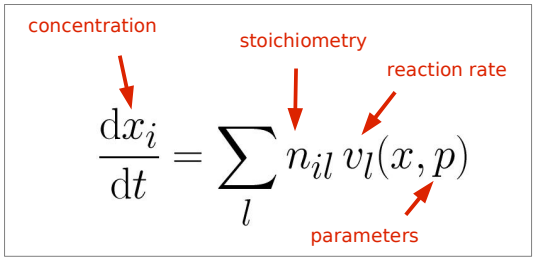
Metabolic control theory



Summary: Modelling formalisms for biochemical systems

Kinetic models





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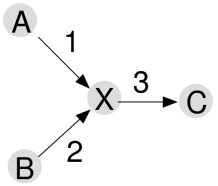
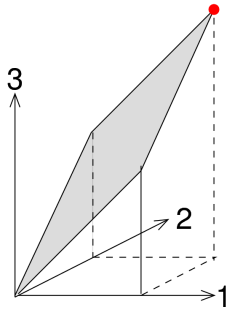
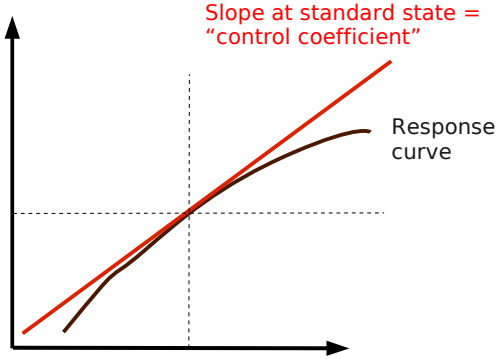




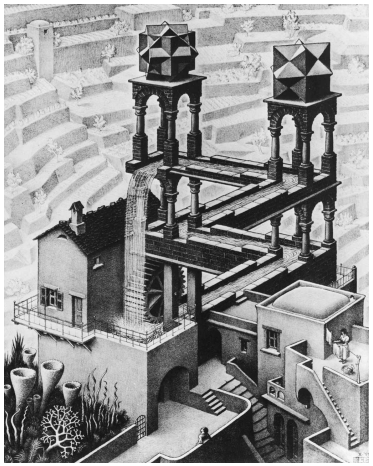
Metabolic control theory

Systemic effect:
flux or concentration



Local cause:
e.g., single enzyme level

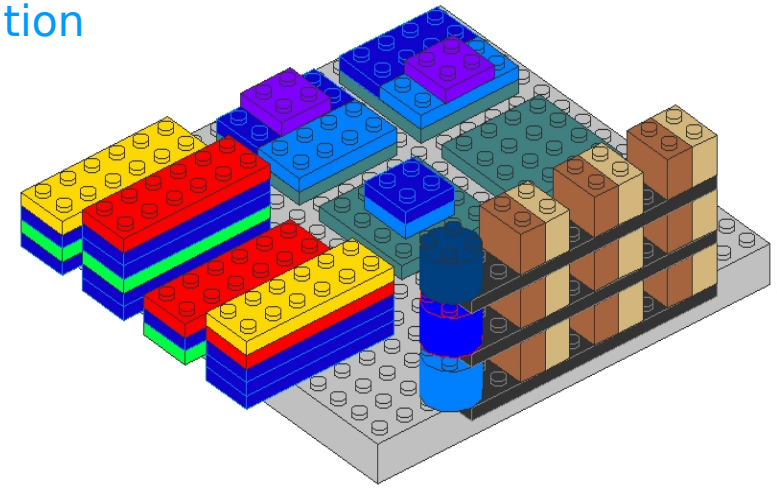
Thermodynamic analysis

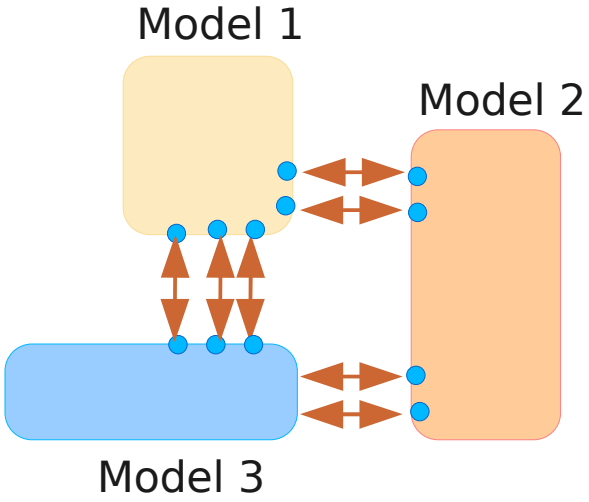


Technical resources for modelling

Playing LEGO with biochemical models ?

Model composition





Playing LEGO with biochemical models ?

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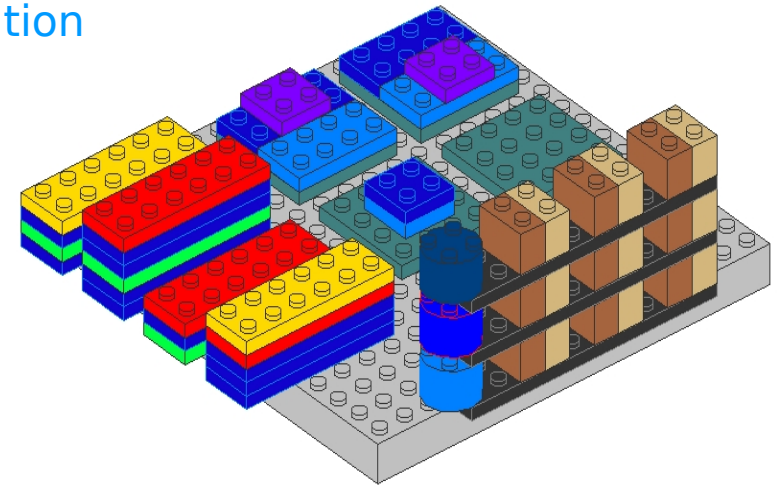
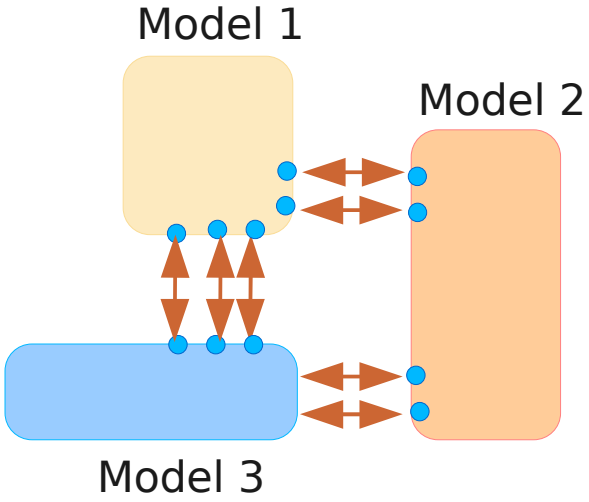
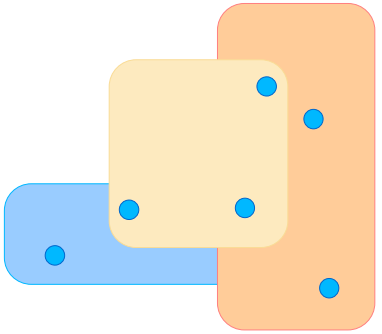




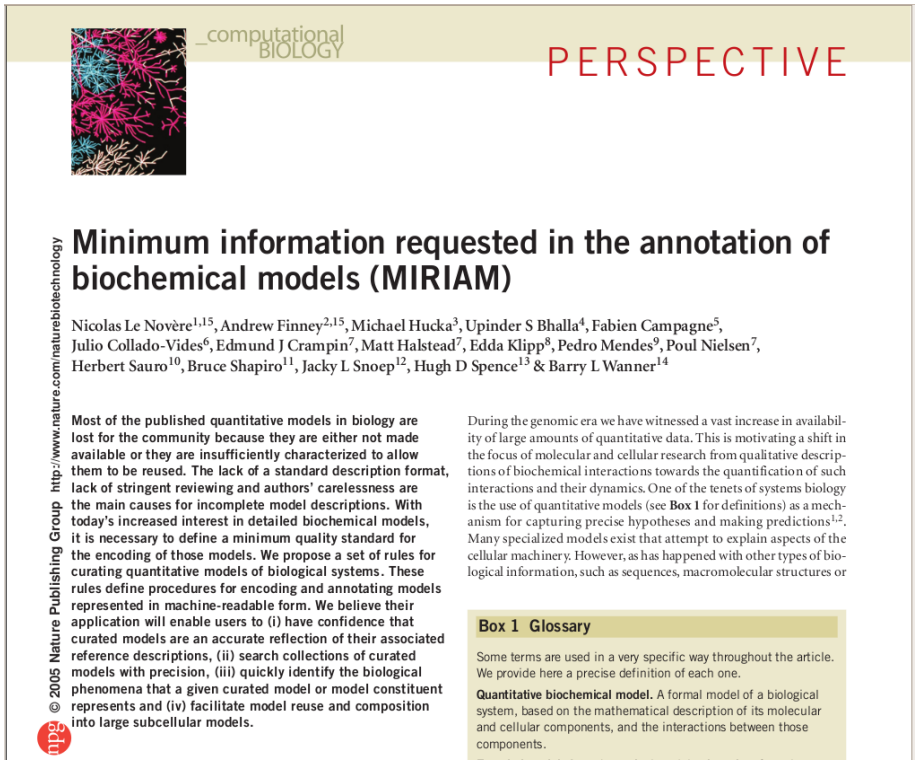
Model merging



Models should be reusable

"Most of the published quantitative models in biology are lost for the community because they are either not made available or they are insufficiently characterized to allow them to be reused."

Le Novere *et al,* (2005)



_computational BIOLOGY

PERSPECTIVE

Minimum information requested in the annotation of biochemical models (MIRIAM)

Nicolas Le Novère[1,15], Andrew Finney[2,15], Michael Hucka[3], Upinder S Bhalla[4], Fabien Campagne[5], Julio Collado-Vides[6], Edmund J Crampin[7], Matt Halstead[7], Edda Klipp[8], Pedro Mendes[9], Poul Nielsen[7], Herbert Sauro[10], Bruce Shapiro[11], Jacky L Snoep[12], Hugh D Spence[13] & Barry L Wanner[14]

Most of the published quantitative models in biology are lost for the community because they are either not made available or they are insufficiently characterized to allow them to be reused. The lack of a standard description format, lack of stringent reviewing and authors' carelessness are the main causes for incomplete model descriptions. With today's increased interest in detailed biochemical models, it is necessary to define a minimum quality standard for the encoding of those models. We propose a set of rules for curating quantitative models of biological systems. These rules define procedures for encoding and annotating models represented in machine-readable form. We believe their application will enable users to (i) have confidence that curated models are an accurate reflection of their associated reference descriptions, (ii) search collections of curated models with precision, (iii) quickly identify the biological phenomena that a given curated model or model constituent represents and (iv) facilitate model reuse and composition into large subcellular models.

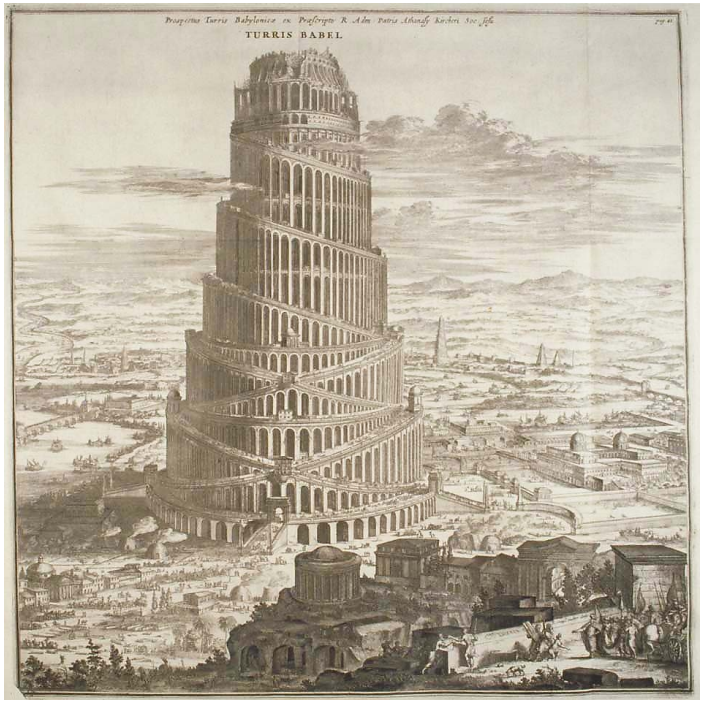
During the genomic era we have witnessed a vast increase in availability of large amounts of quantitative data. This is motivating a shift in the focus of molecular and cellular research from qualitative descriptions of biochemical interactions towards the quantification of such interactions and their dynamics. One of the tenets of systems biology is the use of quantitative models (see **Box 1** for definitions) as a mechanism for capturing precise hypotheses and making predictions[1,2]. Many specialized models exist that attempt to explain aspects of the cellular machinery. However, as has happened with other types of biological information, such as sequences, macromolecular structures or

Box 1 Glossary

Some terms are used in a very specific way throughout the article. We provide here a precise definition of each one.

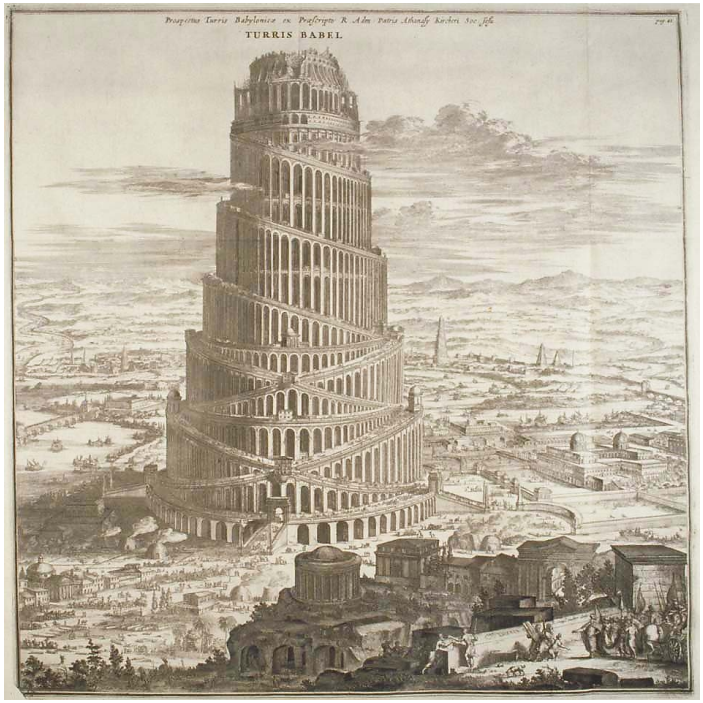
Quantitative biochemical model. A formal model of a biological system, based on the mathematical description of its molecular and cellular components, and the interactions between those components.

Systems Biology Markup Language (SBML)



Systems Biology Markup Language (SBML)

One exchange format -
about 170 tools that understand each other

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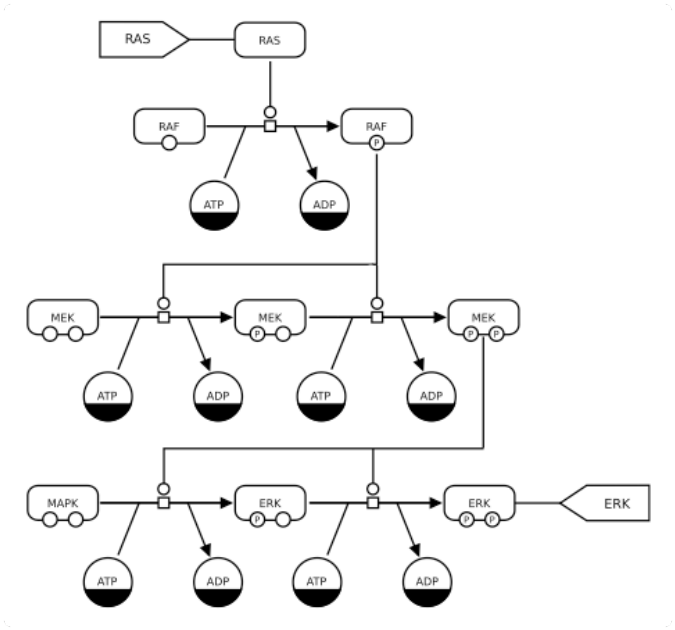
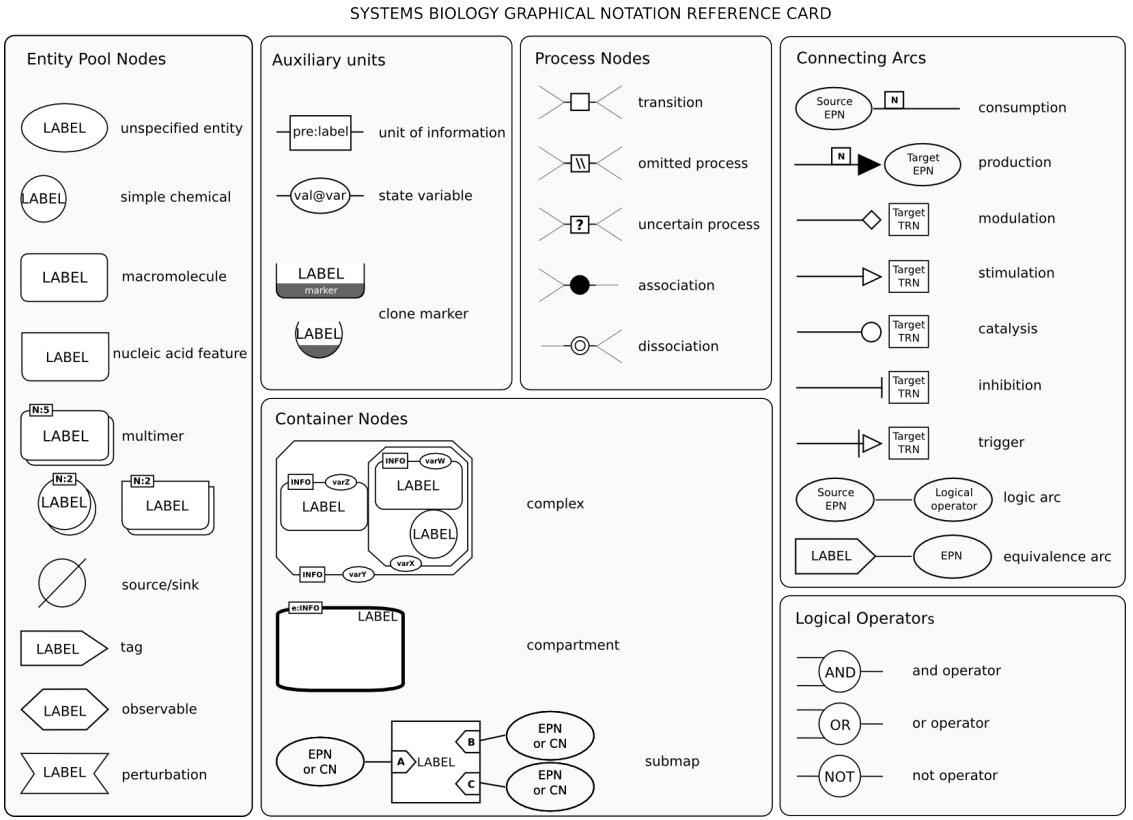
SBML main site http://sbml.org/

Systems Biology Graphical Notation (SBGN)

Process description diagram





SBGN Systems Biology Graphical Notation

http://sbgn.org/

Data, modelling software, and models are available on the web

Network reconstructions

KEGG Kyoto Encyclopedia of Genes and Genomes

BioCyc™ Database Collection

Databases for biological numbers

BRENDA

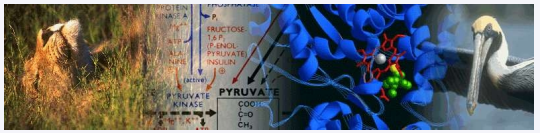
NIST

B10NUMB3R5 THE DATABASE OF USEFUL BIOLOGICAL NUMBERS

Model repositories

BIOMODELS.NET

Database of curated annotated models
http://biomodels.org/

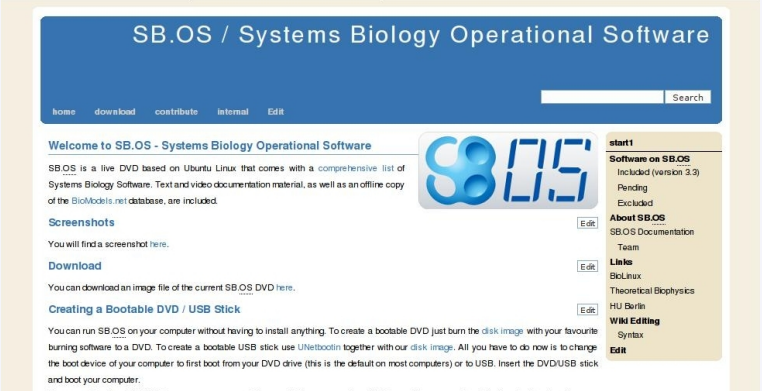


JWS online: database of curated models
http://jjj.biochem.sun.ac.za/

Modelling software

http://sbml.org/ SBML™

SB.OS – Live DVD with free modelling software



www.sbos.eu

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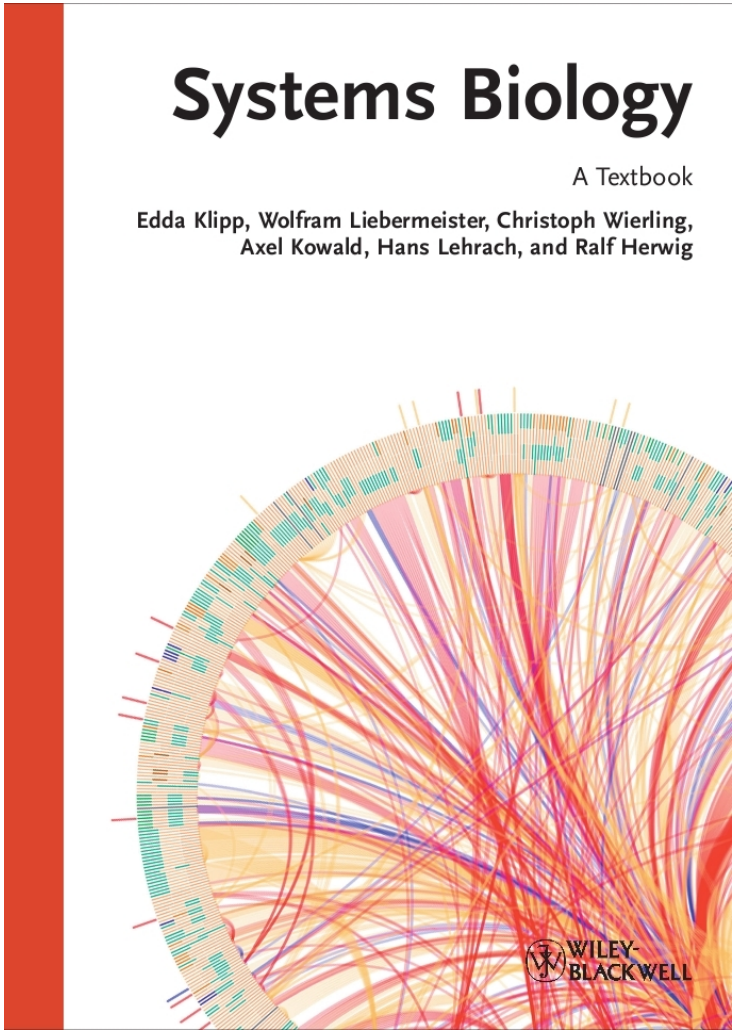

Thank you !