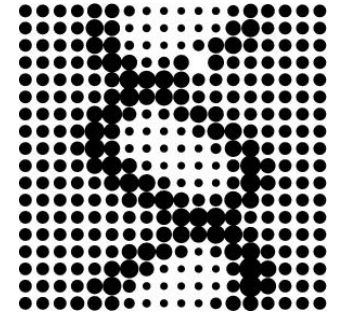


# Modelling and control of biochemical systems

Wolfram Liebermeister  
Max Planck Institute for Molecular Genetics  
Berlin



# Understandability

Modelling and control of biochemical systems

Wolfram Liebermeister  
Max Planck Institute for Molecular Genetics  
Berlin

# Trouble with complex systems

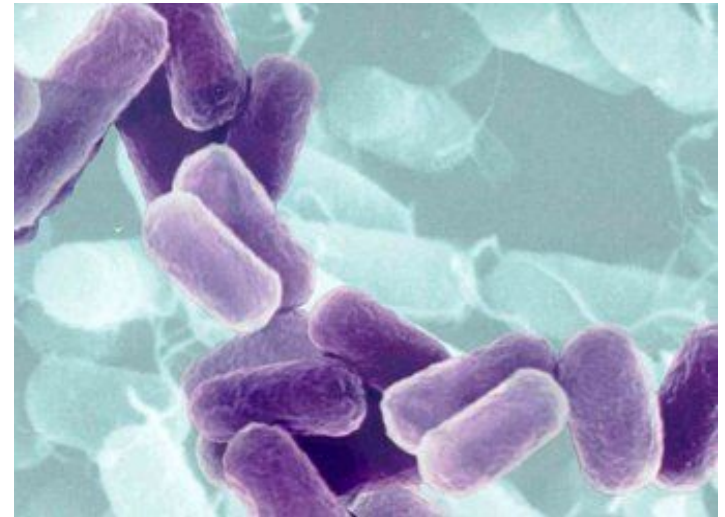
## Things we understand easily

Separate entities

Small numbers

Direct effects

Causal chains



... but living systems are

Continuous

Complex

Dynamic

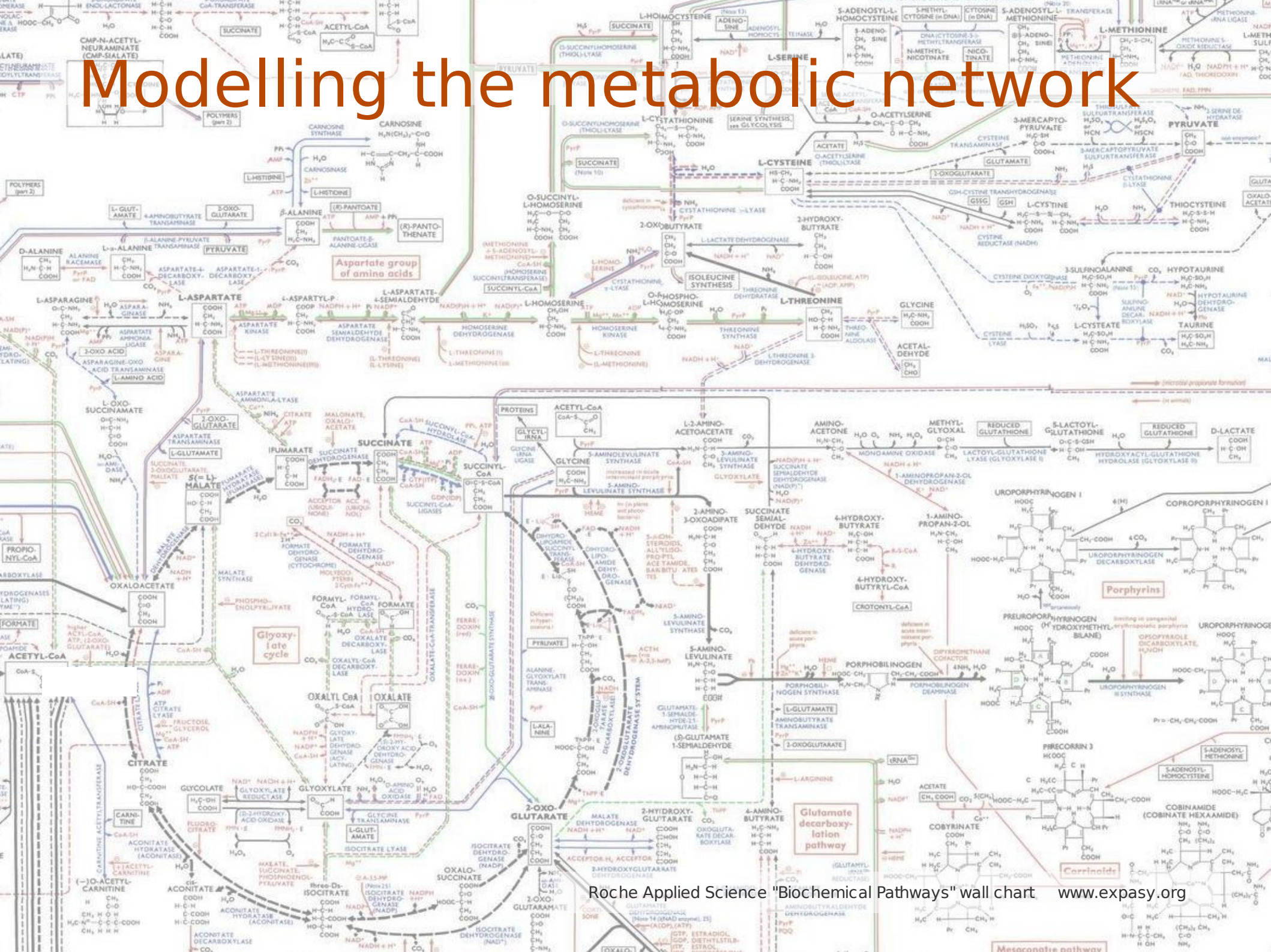
Adaptive

Stochastic

Evolved

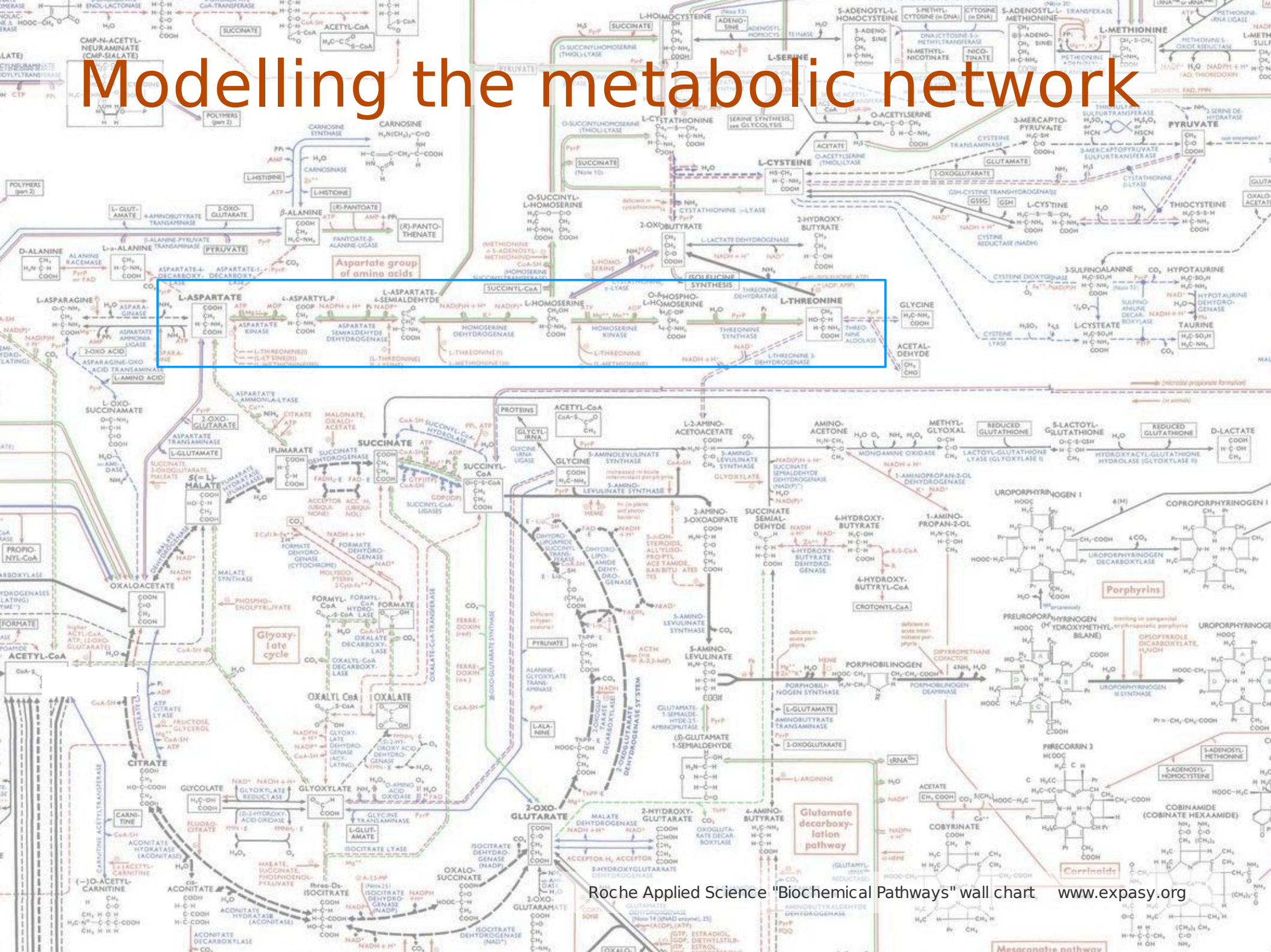


# Modelling the metabolic network



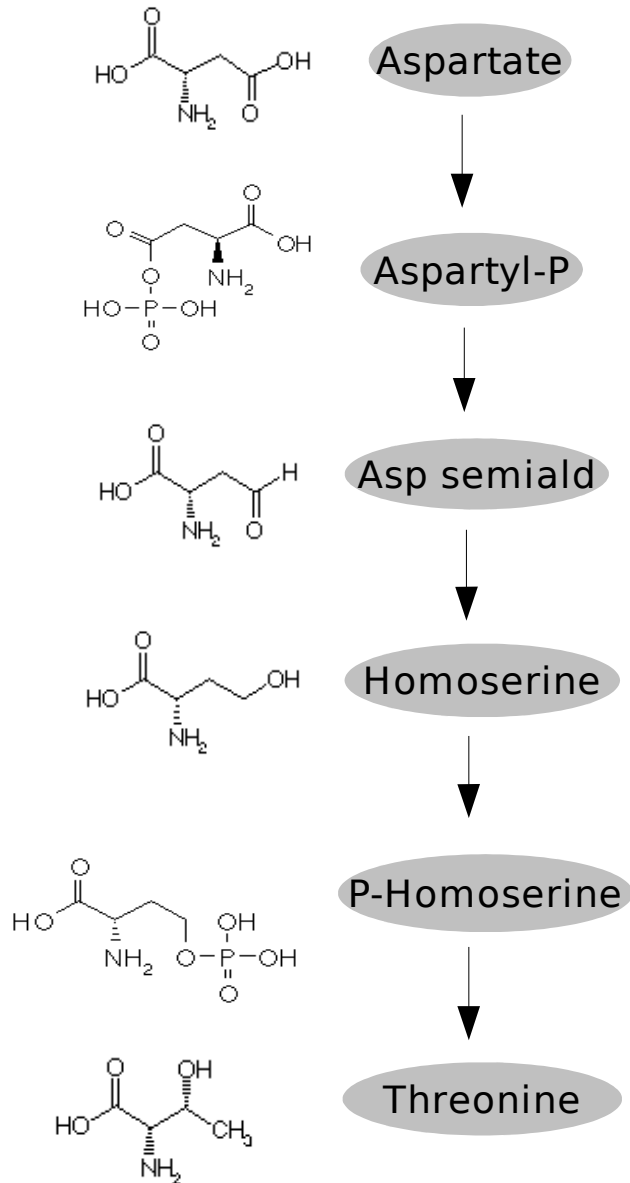


# Modelling the metabolic network



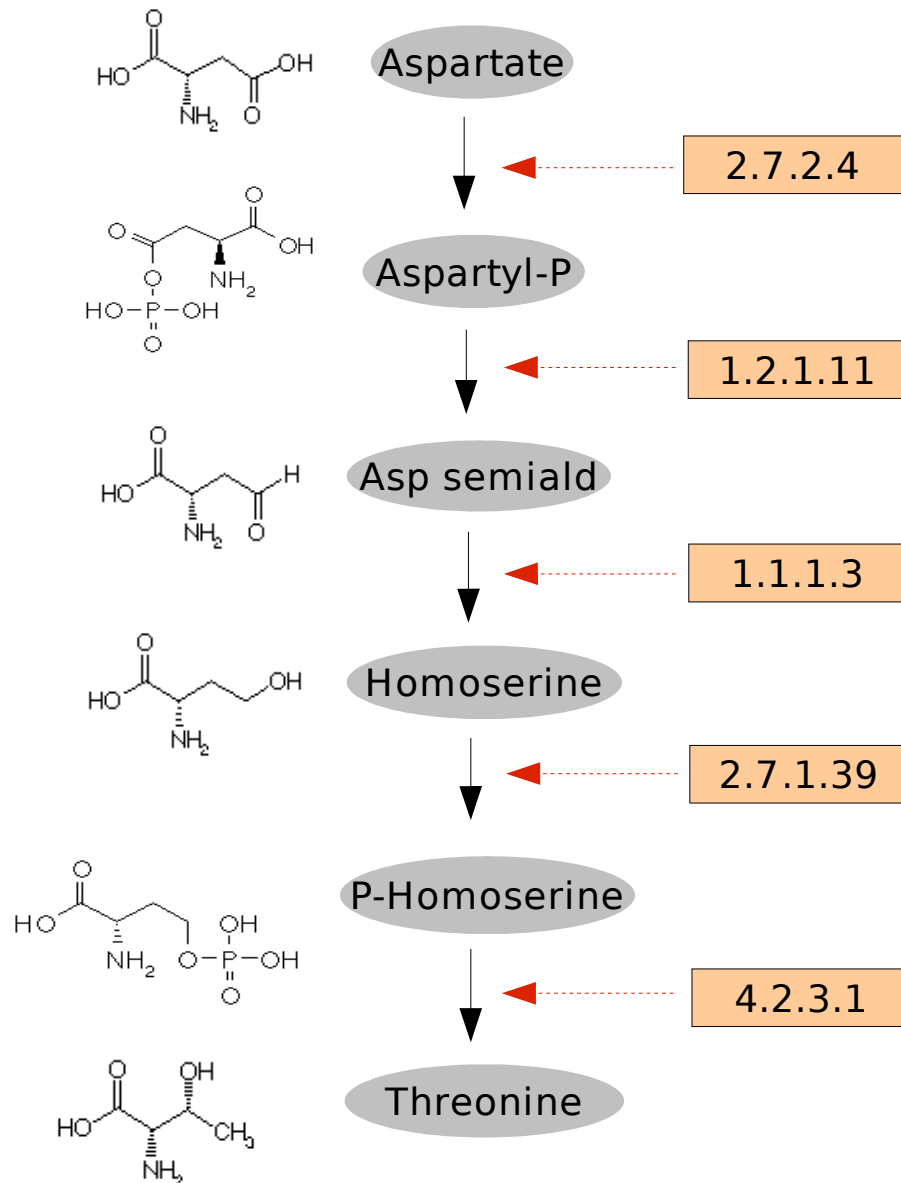
# Anatomy of a metabolic system

## Threonine pathway in E. Coli



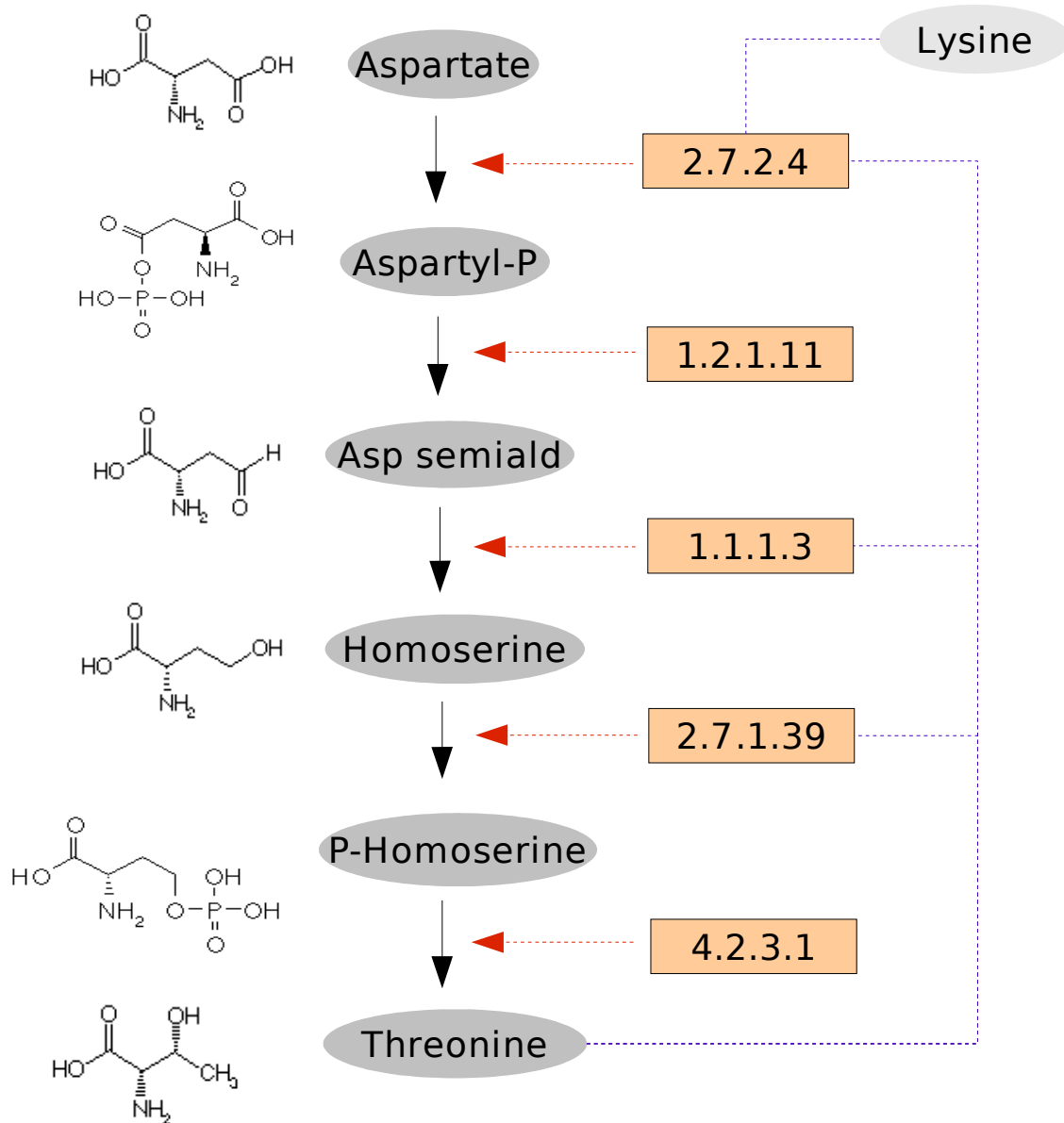
# Anatomy of a metabolic system

## Threonine pathway in E. Coli



# Anatomy of a metabolic system

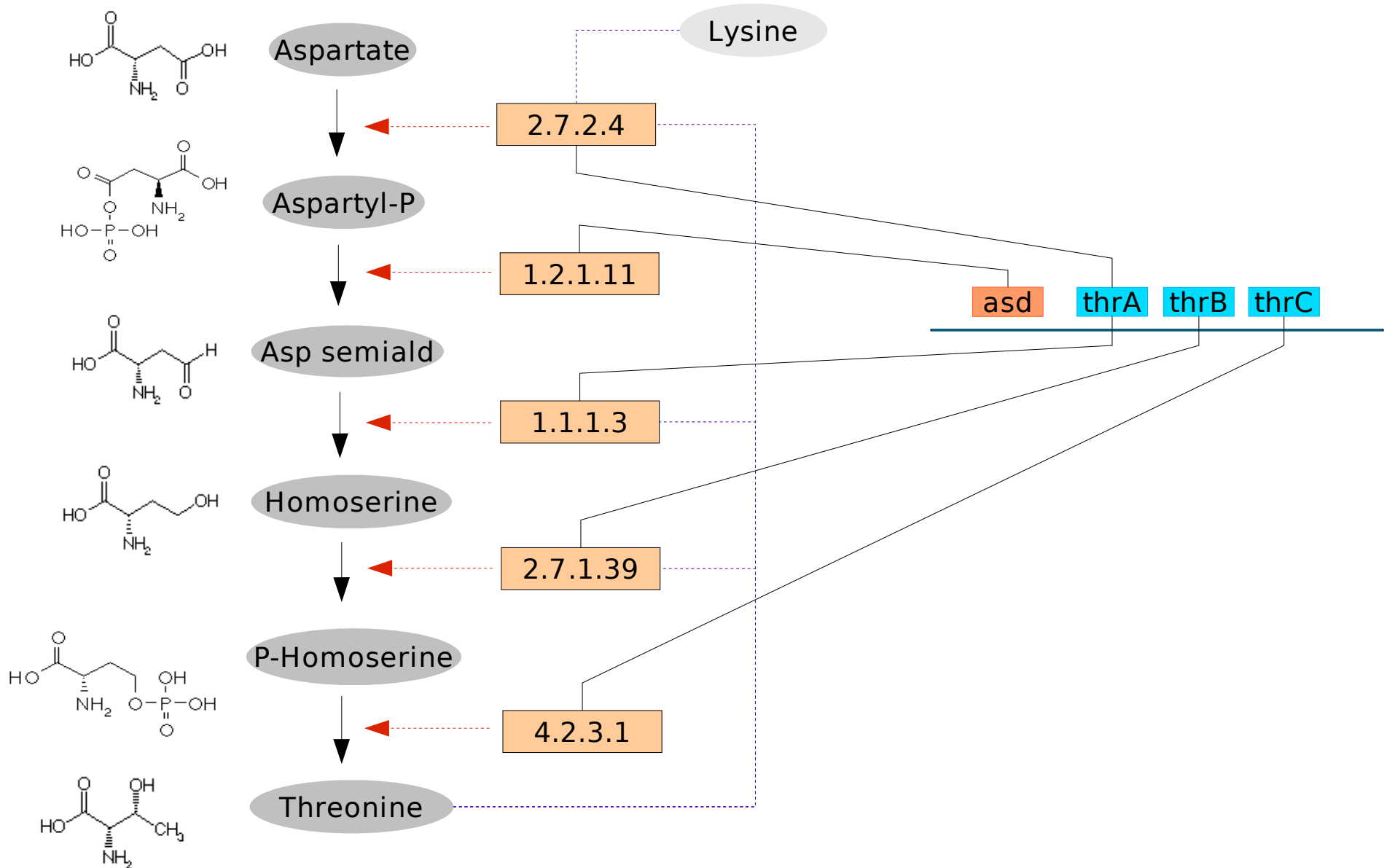
## Threonine pathway in E. Coli





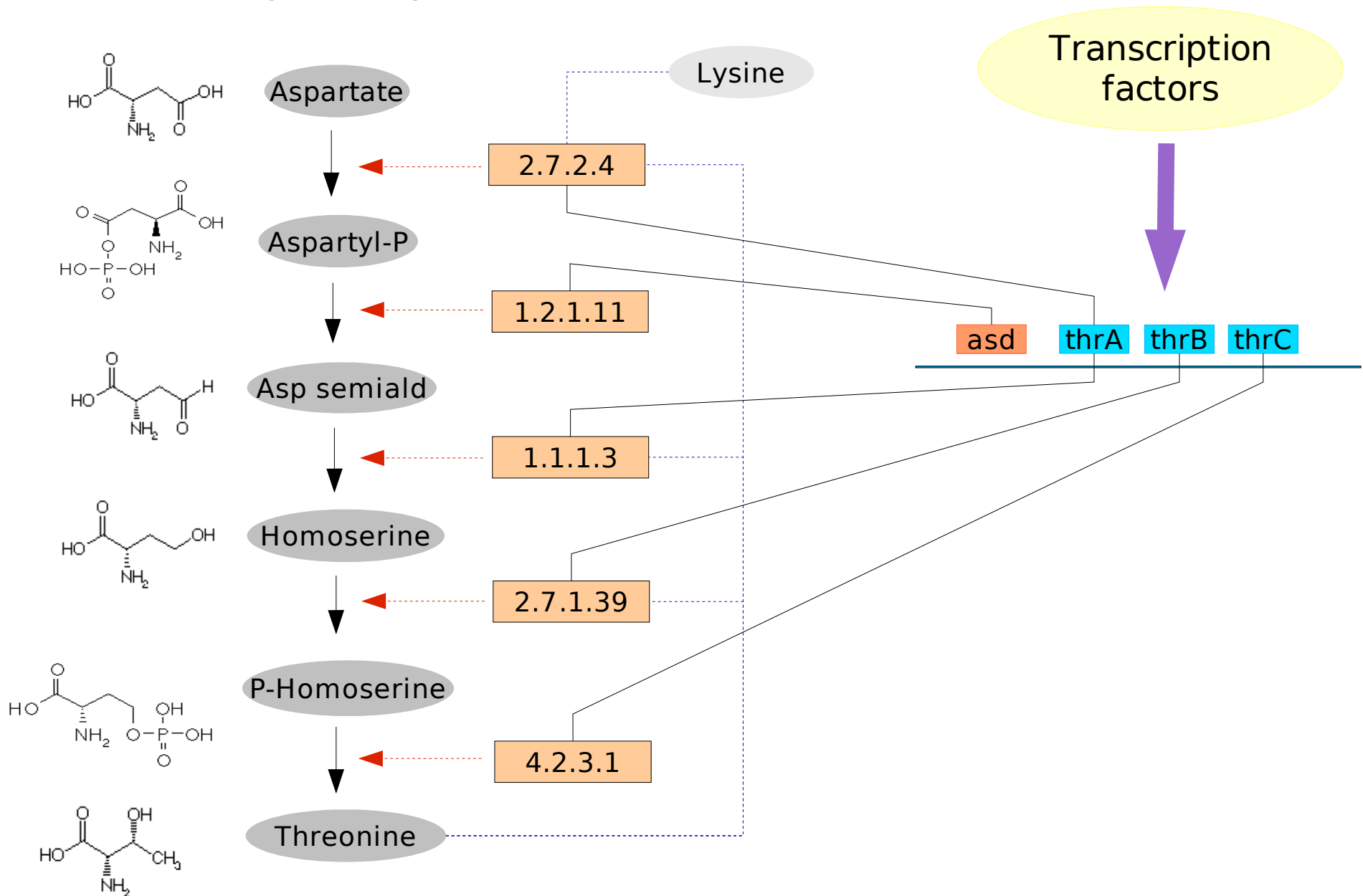
# Anatomy of a metabolic system

## Threonine pathway in E. Coli



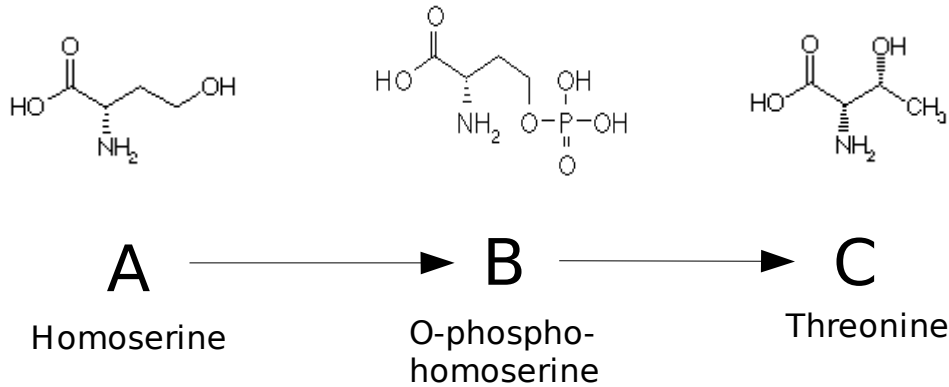
# Anatomy of a metabolic system

## Threonine pathway in E. Coli



# Dynamic laws for metabolic networks

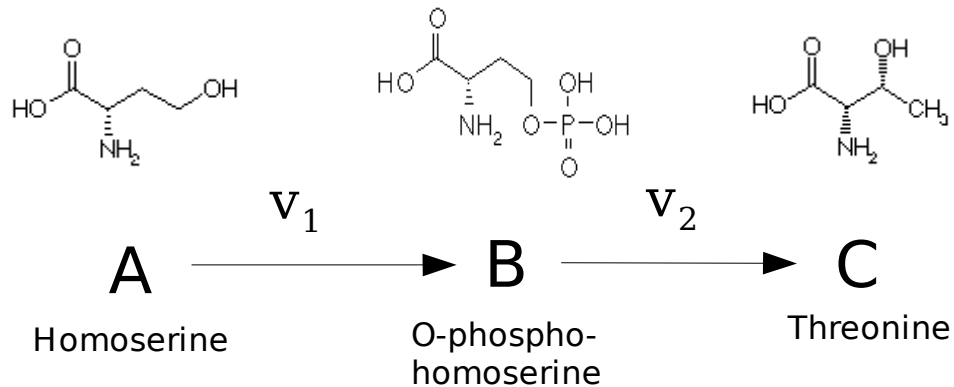
derived from balance of concentrations





# Dynamic laws for metabolic networks

derived from balance of concentrations



Reaction velocities

$$v_1 = v_1(a, b)$$

$$v_2 = v_2(b, c)$$

Balance equations

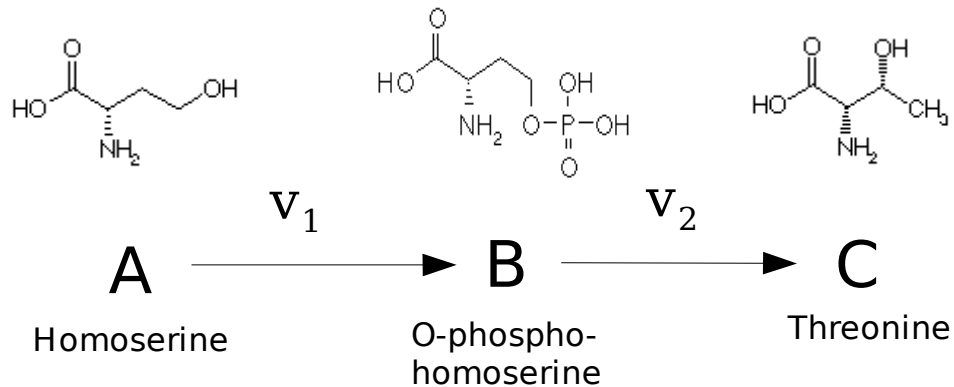
$$da/dt = -v_1$$

$$db/dt = v_1 - v_2$$

$$dc/dt = v_2$$

# Dynamic laws for metabolic networks

derived from balance of concentrations



Reaction velocities

$$v_1 = v_1(a, b)$$

$$v_2 = v_2(b, c)$$

Balance equations

$$da/dt = -v_1$$

$$db/dt = v_1 - v_2$$

$$dc/dt = v_2$$

$$\frac{dx_i}{dt} = \sum_k n_{ik} v_k(\vec{x}, \vec{p})$$

concentration change

stoichiometric coefficient

kinetic law for reaction velocity

all concentrations

all kinetic parameters

# Levels of modelling in systems biology

## 1. Pathway analysis

Flux balance, substance transformation,...

## 2. Kinetic modelling

Parameter fitting, model selection,...

## 3. Control and bifurcation analysis

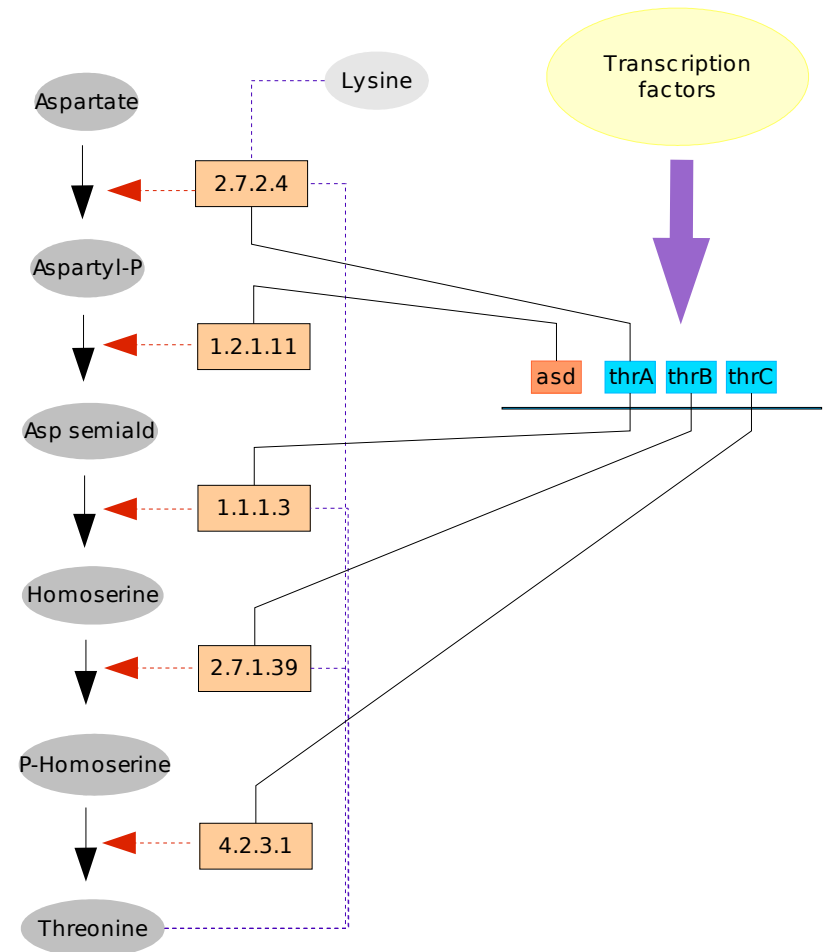
Sensitivities, qualitative behaviour, ...

## 4. Optimality / Shaping by evolution

Robust design, cost-benefit calculation,...

## 5. Model integration

Modularisation, experimental standards,...





# Essential views on complex systems

Modularity

Control analysis

Global modes



# Modularity

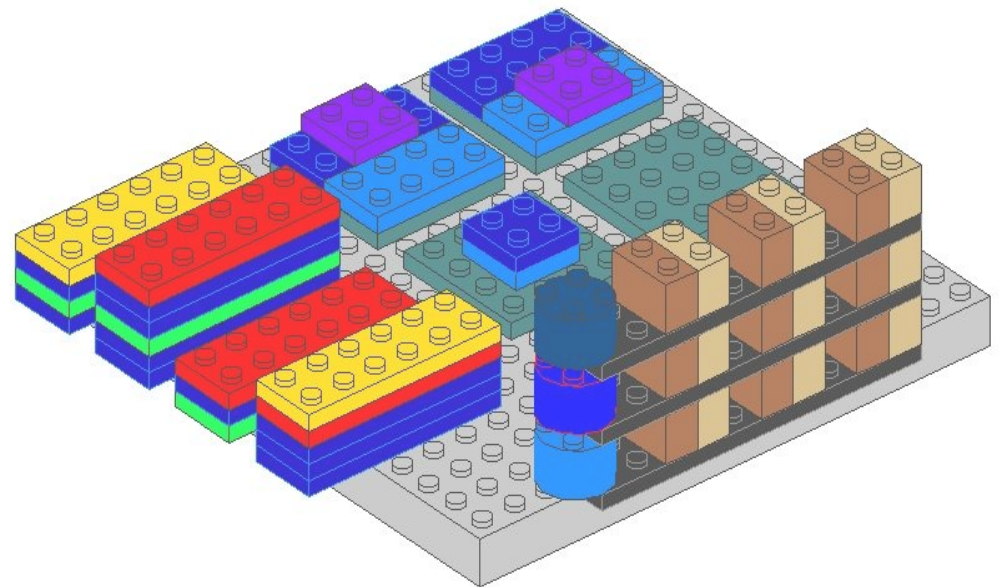
# Modularity

Basic assumption in natural sciences

Many biological systems look modular  
(and many don't)

The whole is more .. is more  
than the sum of its parts

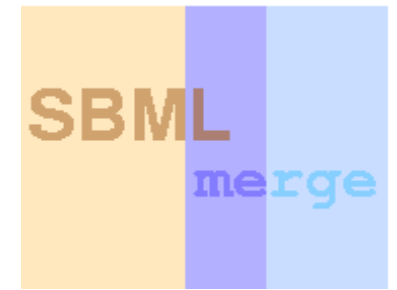
Modular modelling calls  
for experimental standards



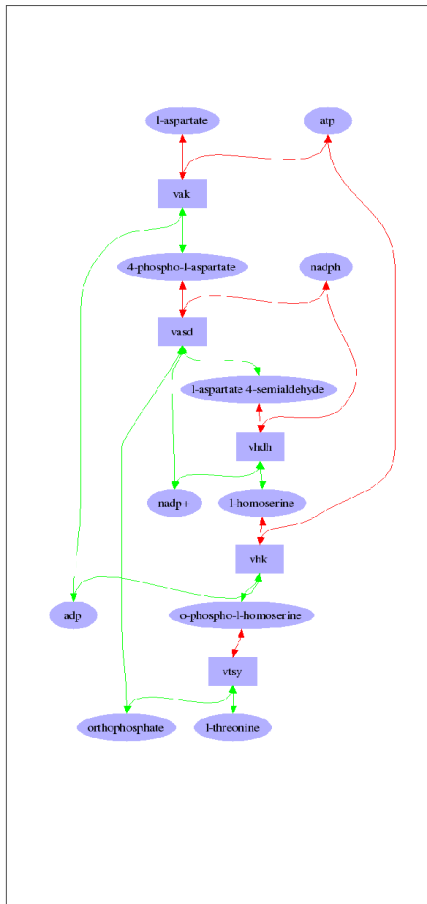


# SBMLmerge

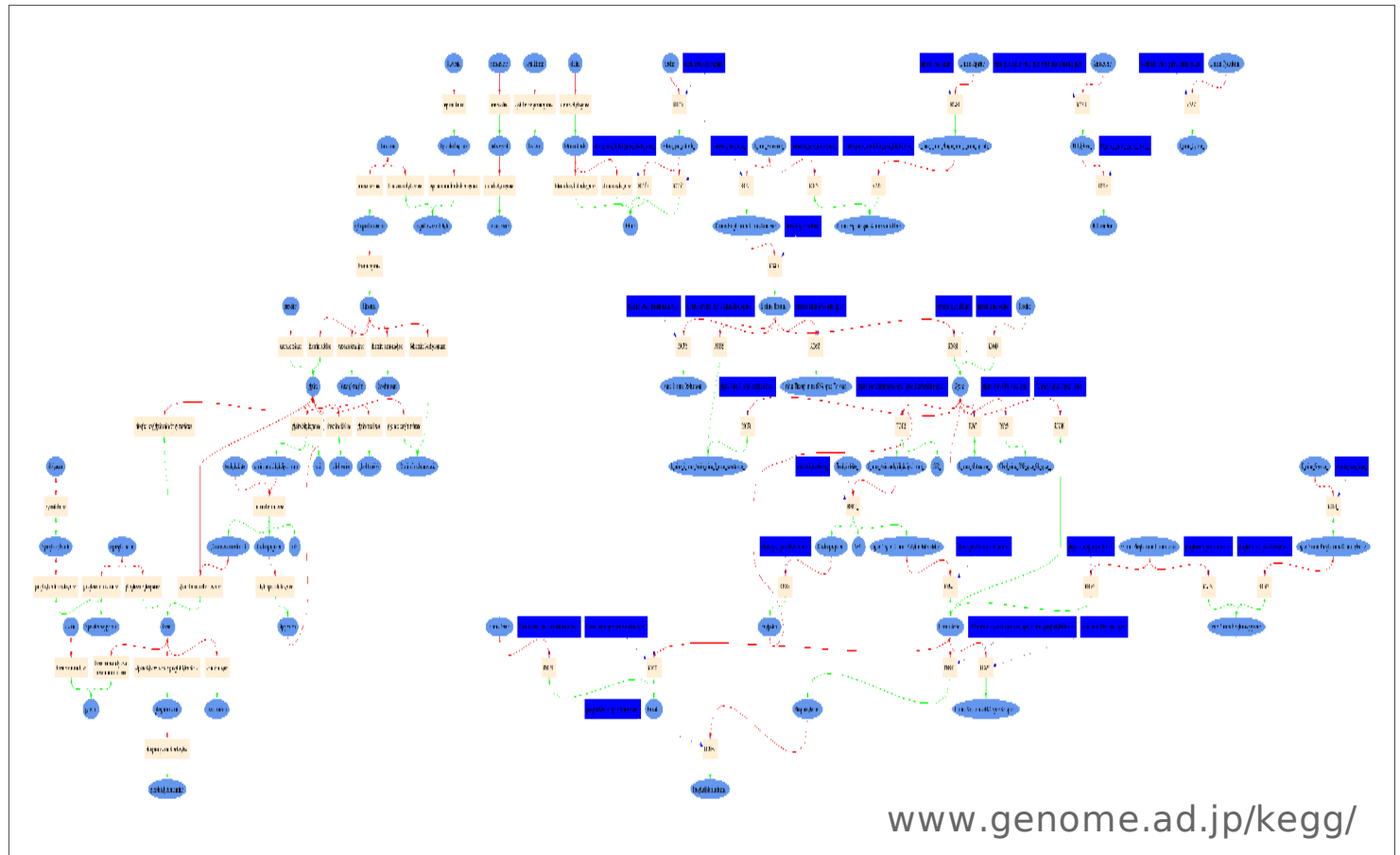
for computer-assisted model integration



Threonine pathway



KEGG chart "Glycine, serine and threonine metabolism"



[www.genome.ad.jp/kegg/](http://www.genome.ad.jp/kegg/)

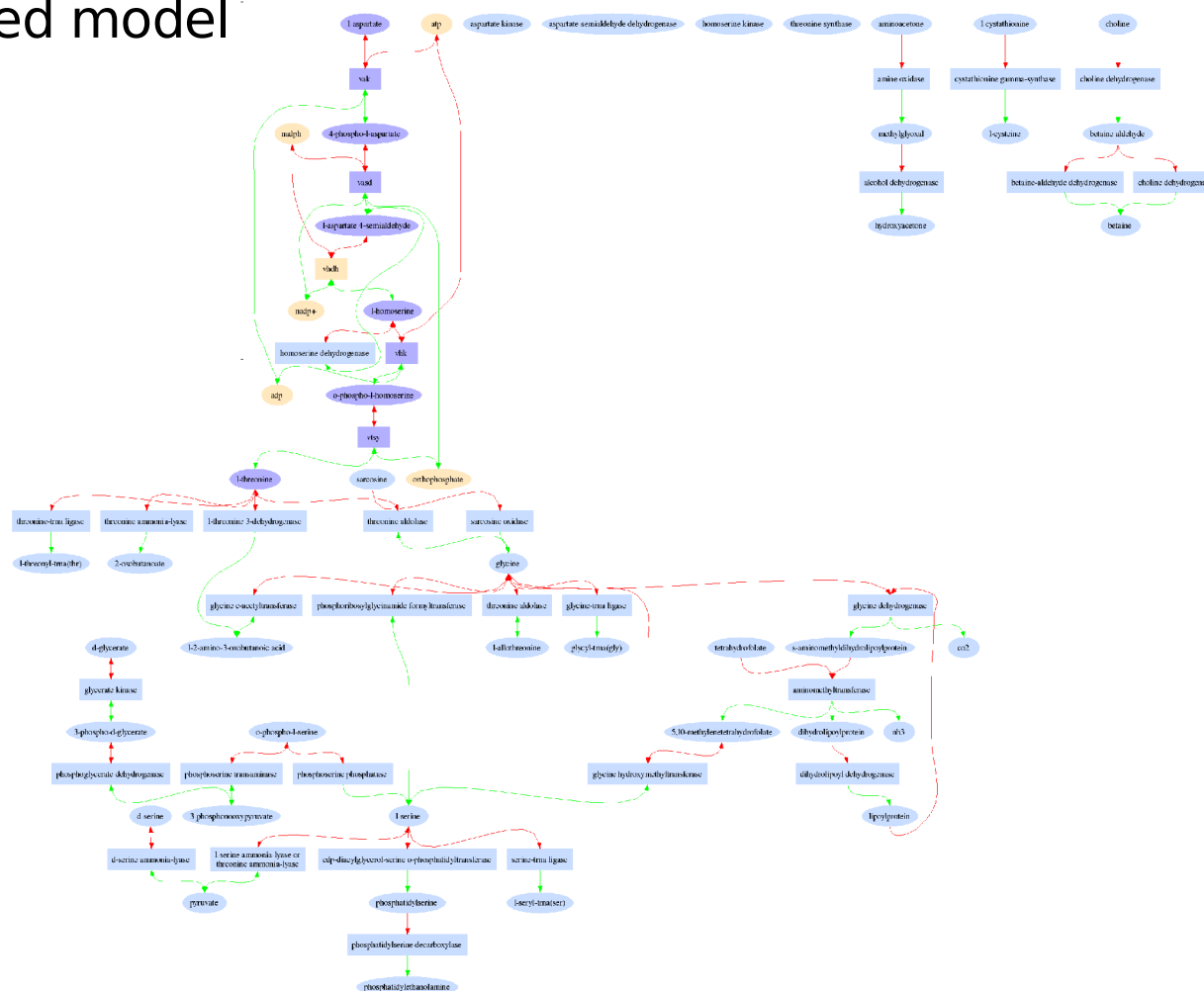
<http://sysbio.molgen.mpg.de/SBMLmerge/>

# SBMLmerge

for computer-assisted model integration

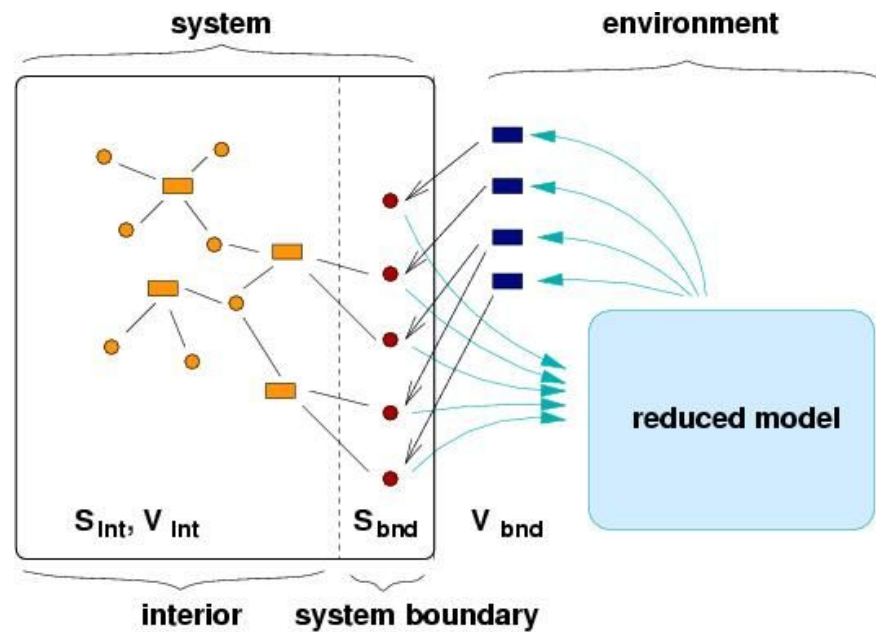
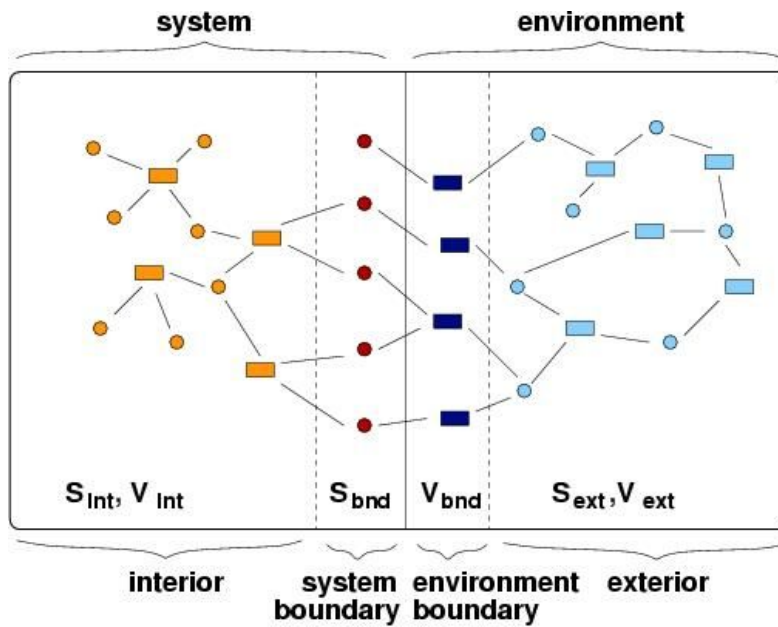


## Merged model



# Turn modules into simple black boxes

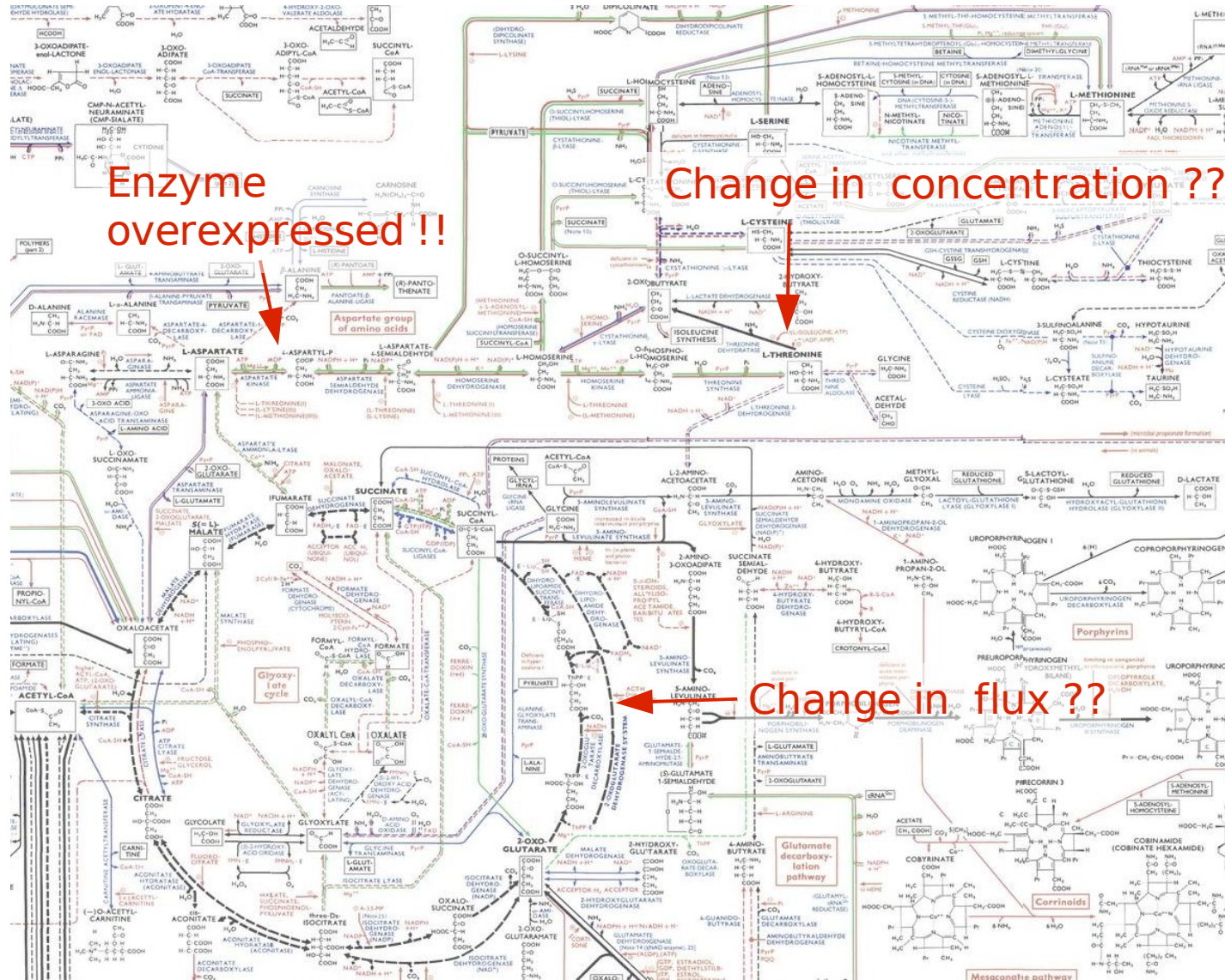
Model reduction by balanced truncation



# Sensitivity analysis

# Metabolic control theory

## Overall effects of local perturbations

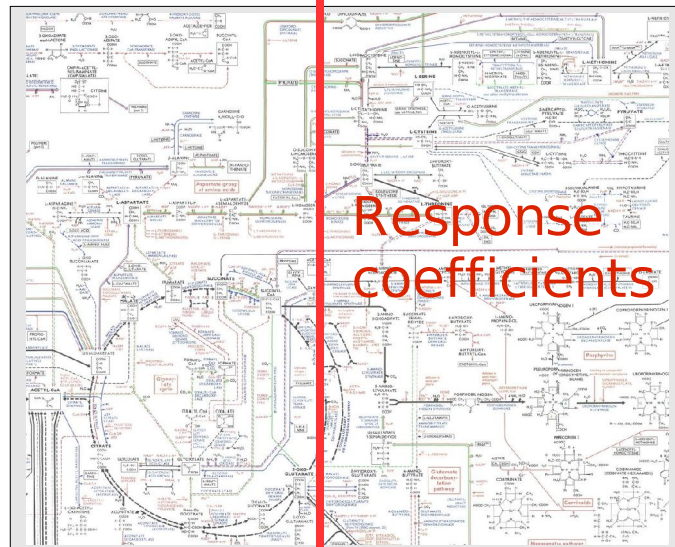


# Metabolic response coefficients

Summarising the infinite causal chains

Parameter change  
One enzyme overexpressed...

$$\Delta p_m$$



Metabolic change  
Altered concentrations?  
Redirected fluxes?

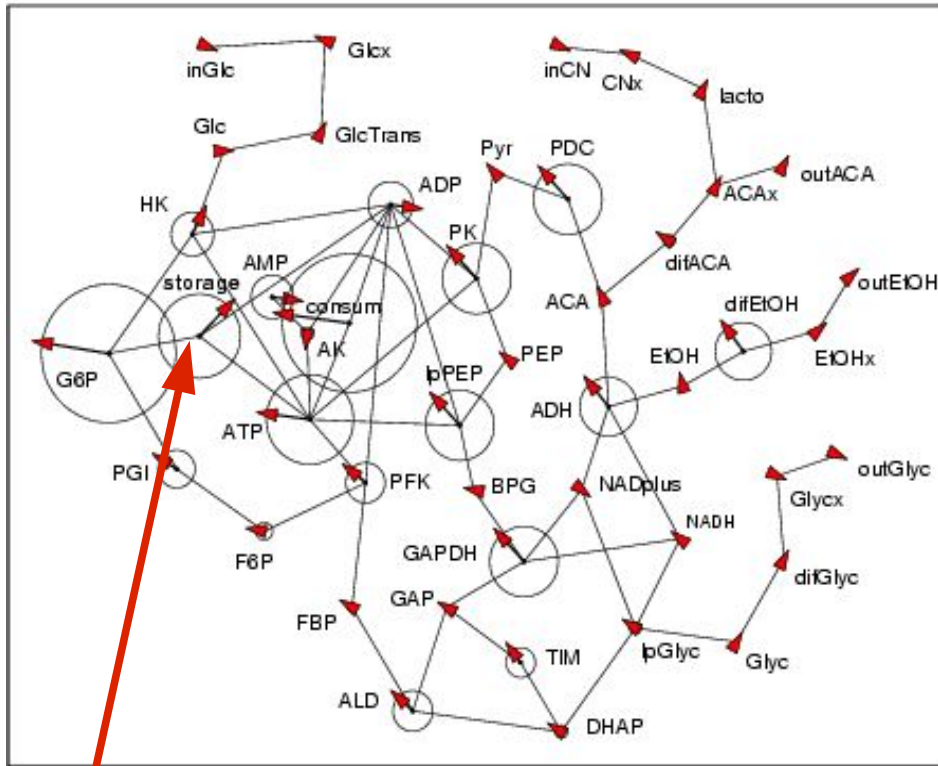
First-order approximation

$$\Delta s_i \approx R_{p_m}^{s_i} \Delta p_m$$



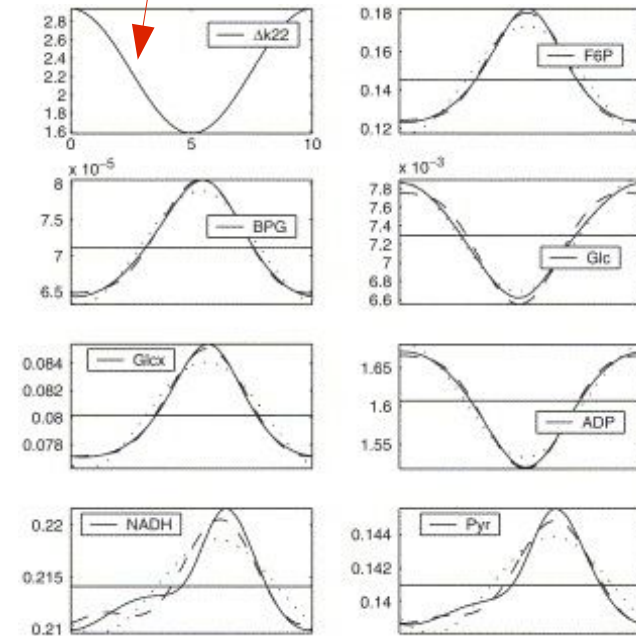
# Spectral response coefficients

Systemic response to forced oscillations



Perturbed  
Reaction

Sine wave  
Perturbation



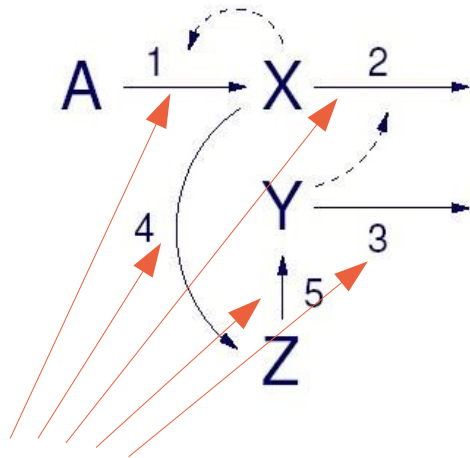
W. Liebermeister (2005), J. Theor. Biol. 234 (3), 423-438

Yeast glycolysis model: F. Hynne et al (2001), Bioph. Chem. 2001 94 (1-2), 121-63

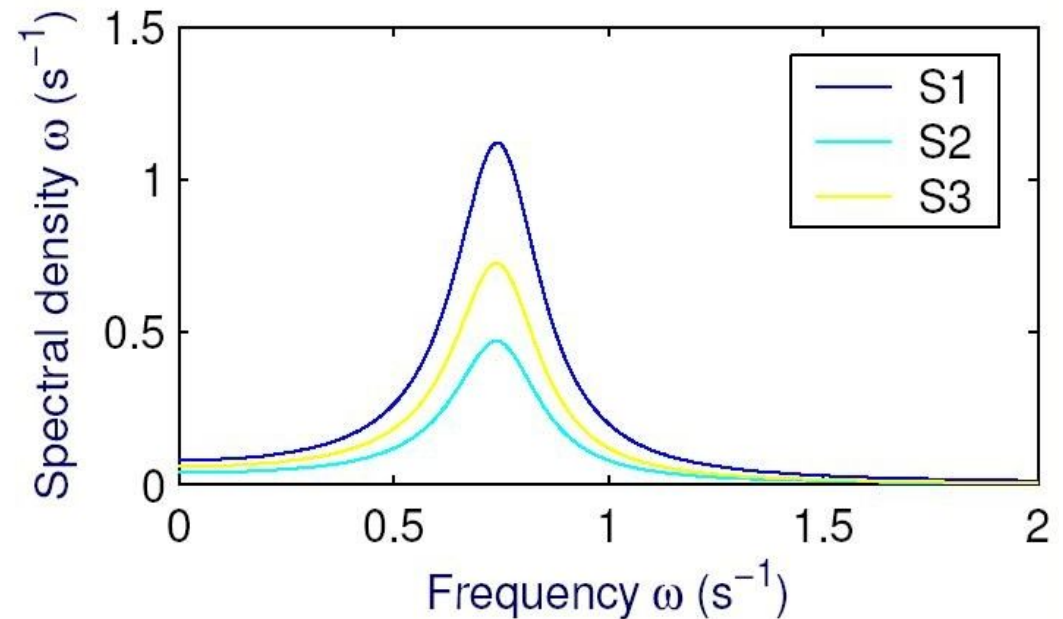
# Spectral response coefficients

Resonance in noise spectra: a systemic property

Feedback system  
below Hopf bifurcation



Intrinsic noise  
due to small particle numbers



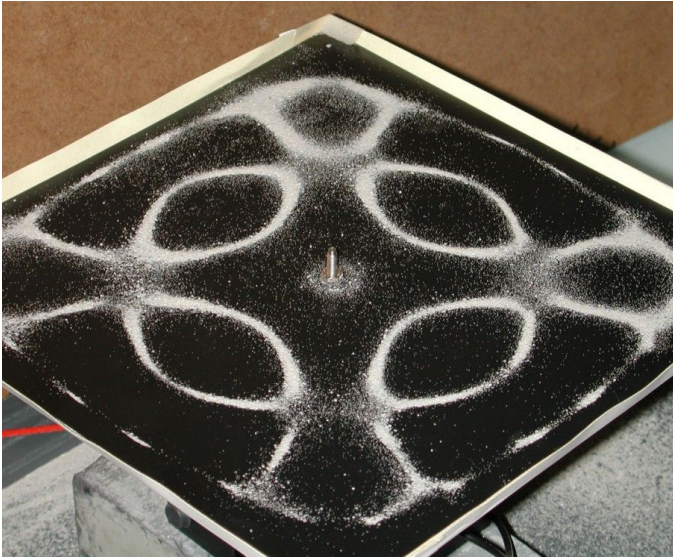
W. Liebermeister (2005), J. Theor. Biol. 234 (3), 423-438

Network model: T. Wilhelm and R. Heinrich, J. Math. Chem. 17 (1995), 1-14

# Modes of collective behaviour

# Global modes in complex systems

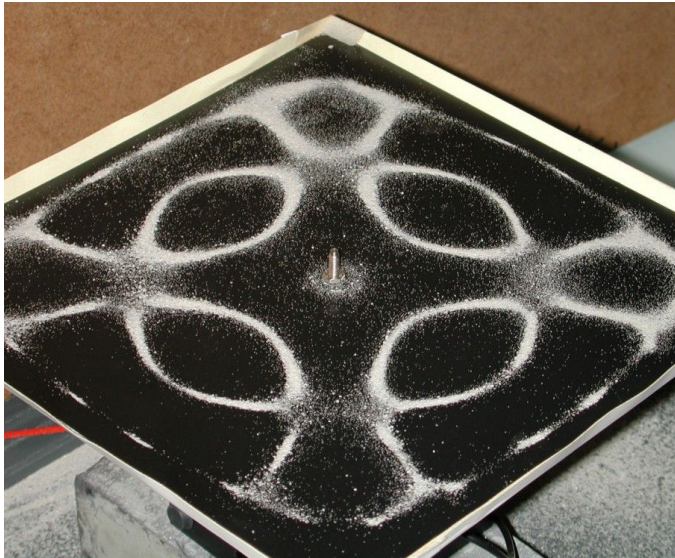
Effective variables to describe collective motion



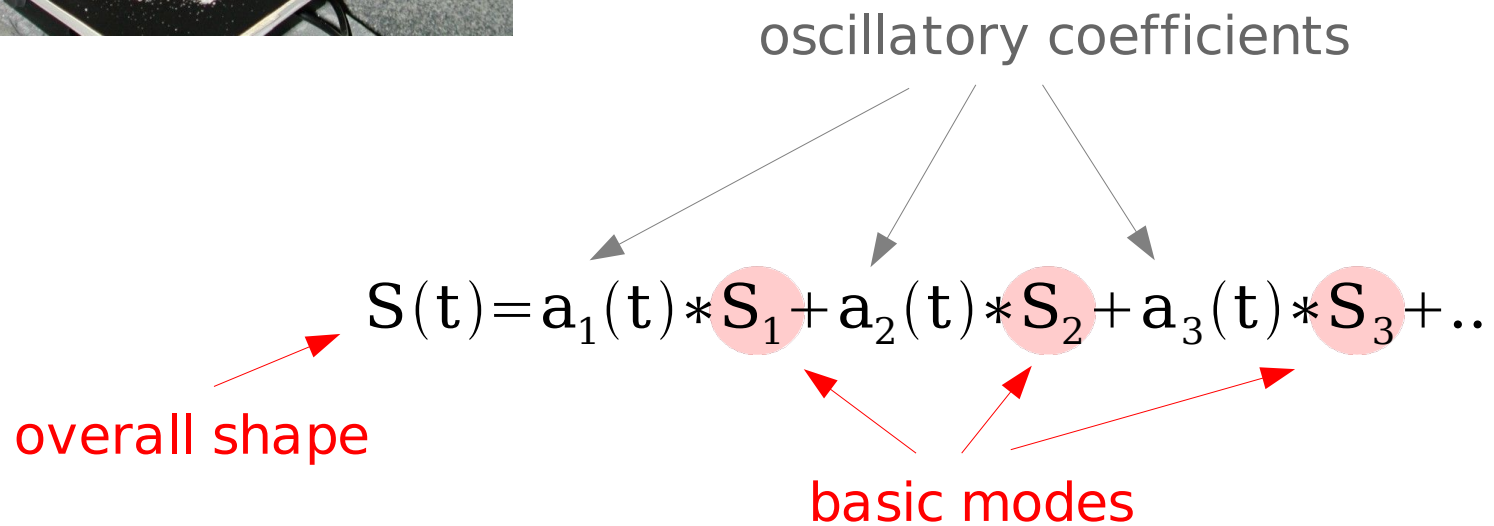
Vibration mode of an elastic plate

# Global modes in complex systems

Effective variables to describe collective motion

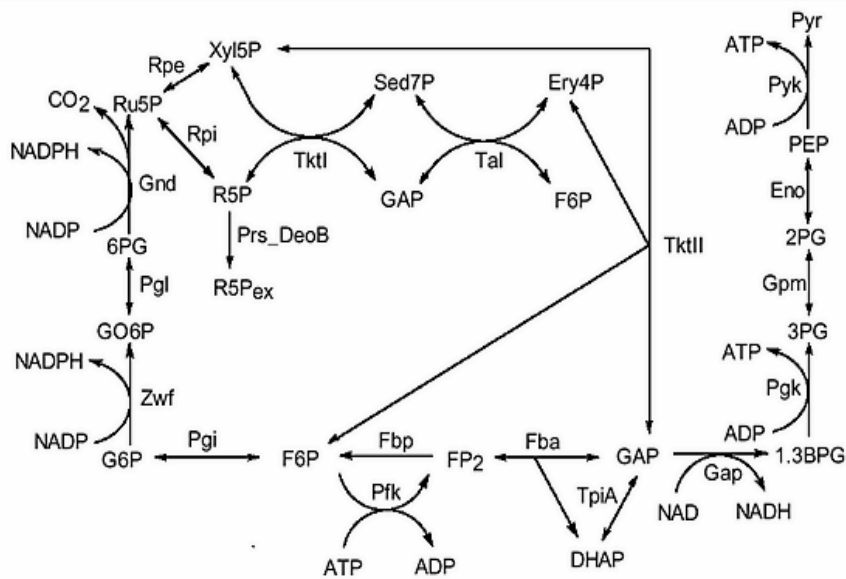


Vibration mode of an elastic plate



# Elementary flux modes

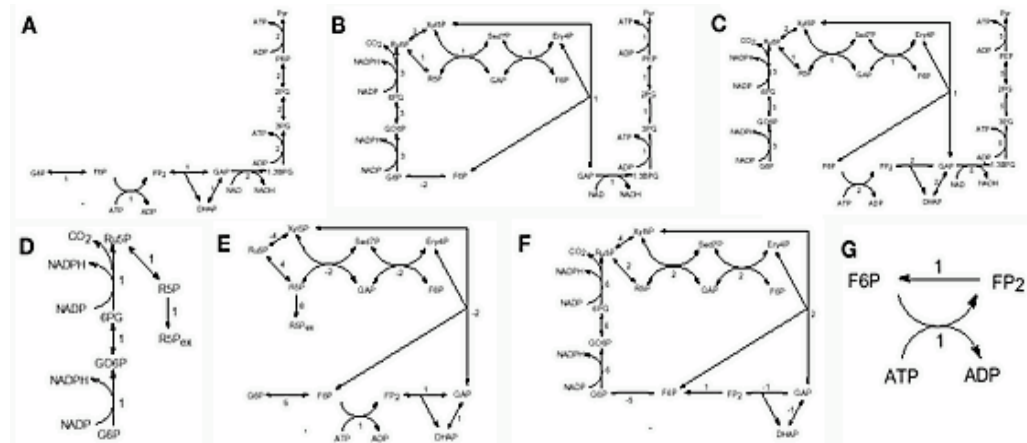
A quantitative definition for metabolic pathways



Flux distribution

$$\vec{v} = a_1 \vec{k}_1 + a_2 \vec{k}_2 + \dots$$

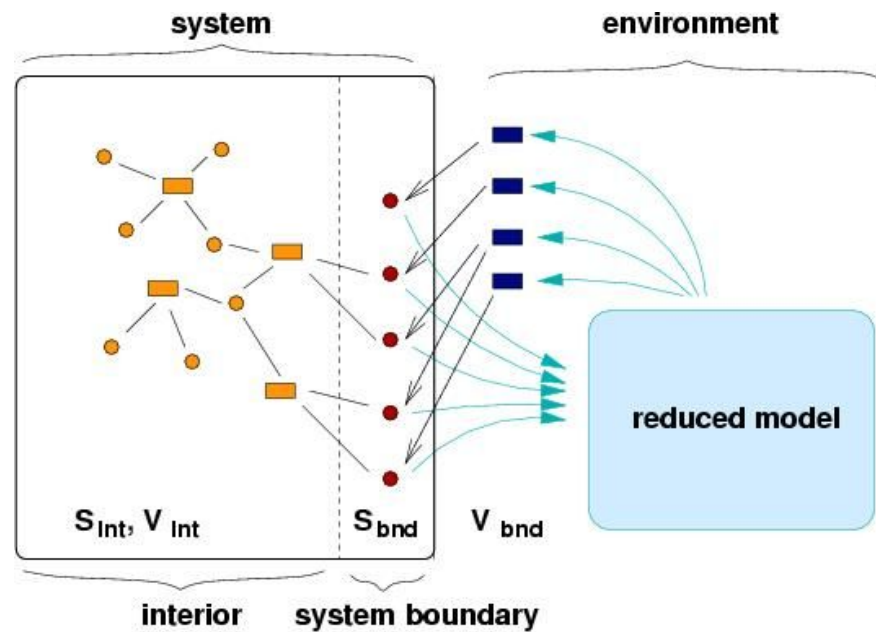
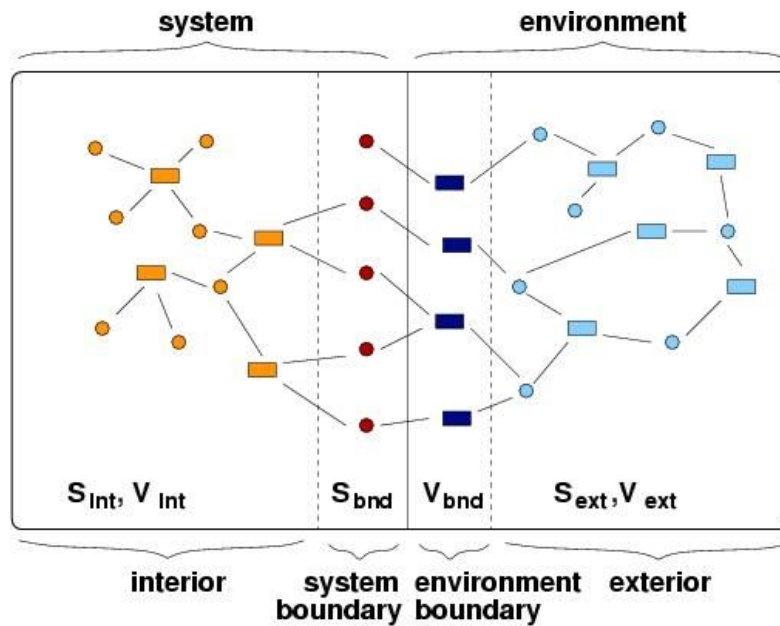
Elementary modes





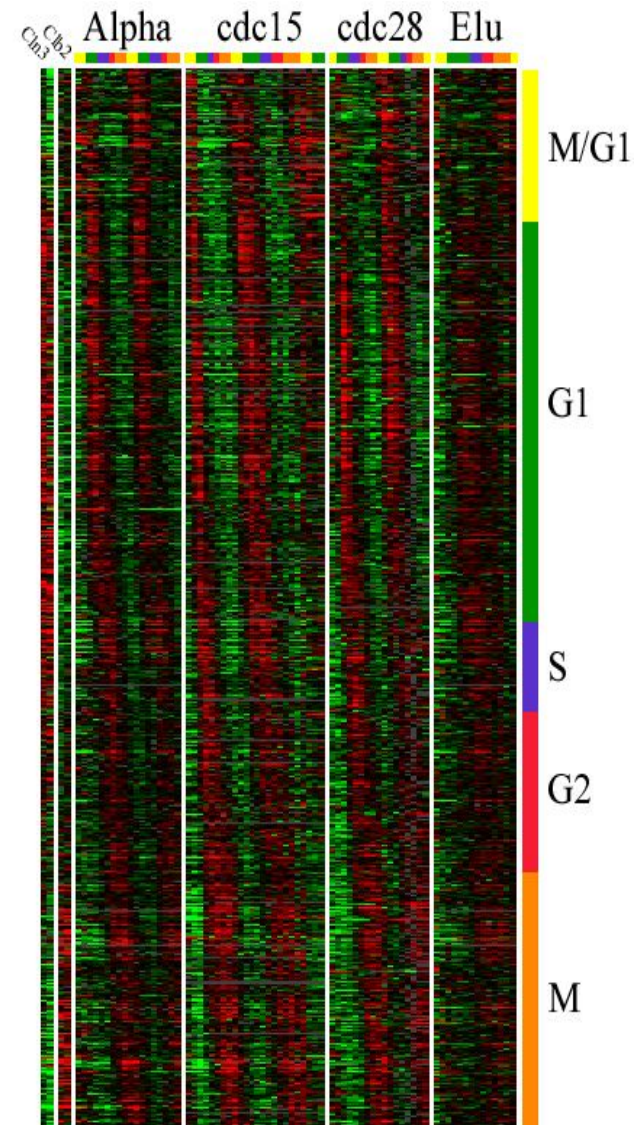
# Model reduction is based on collective modes

Balanced truncation preserves only the dominant global behaviour



# Global modes in microarray data

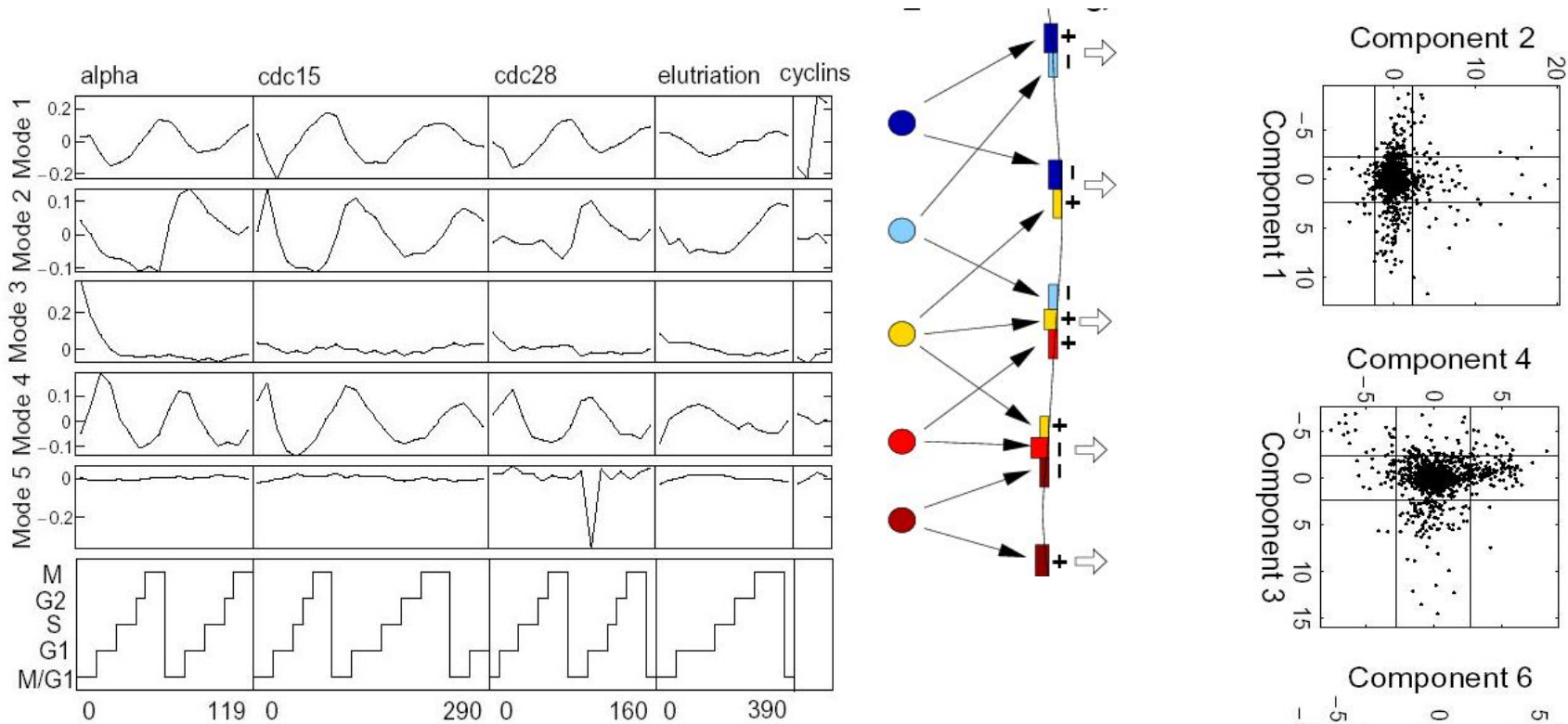
Gene expression during the cell cycle



Data from:  
P. Spellman et al (1998), Mol. Biol. Cell 9, 3273-3297

# Global modes in microarray data

## Independent component analysis



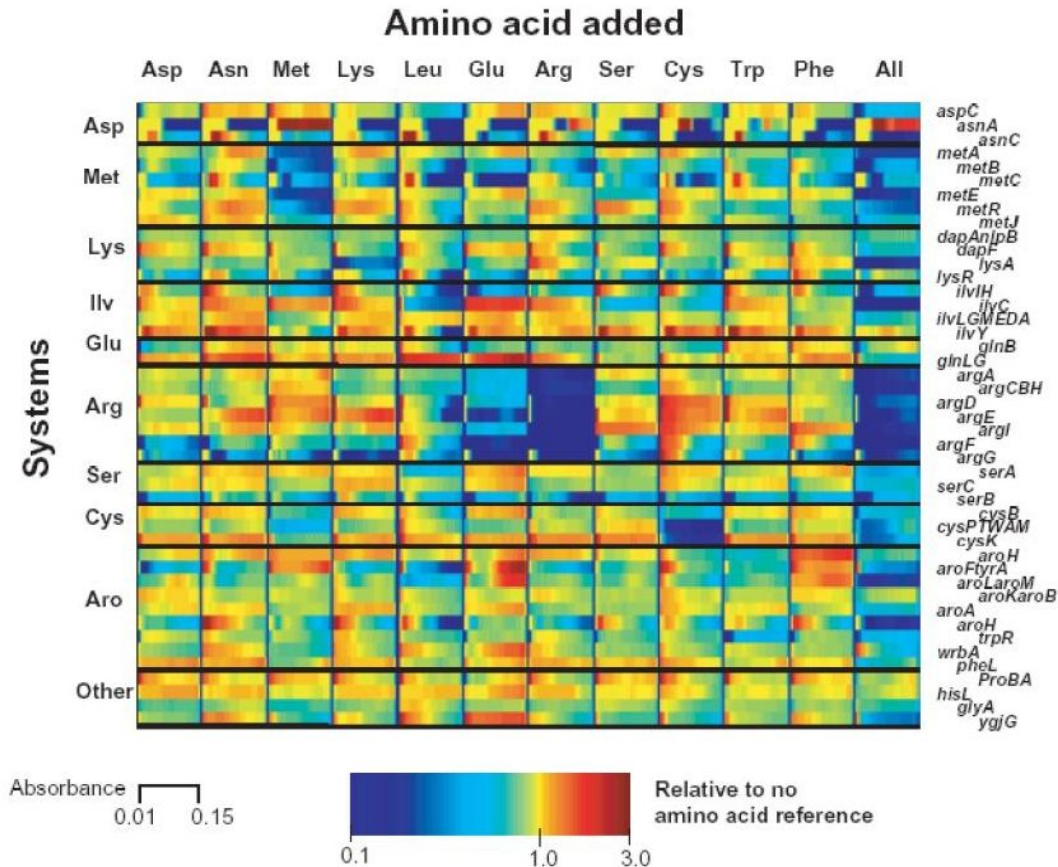
Gene profile

$$x_i(t) = m_1(t) a_{i1} + m_2(t) a_{i2} + \dots$$

Components

# Network component analysis

Global modes reflect the activity of transcription factors



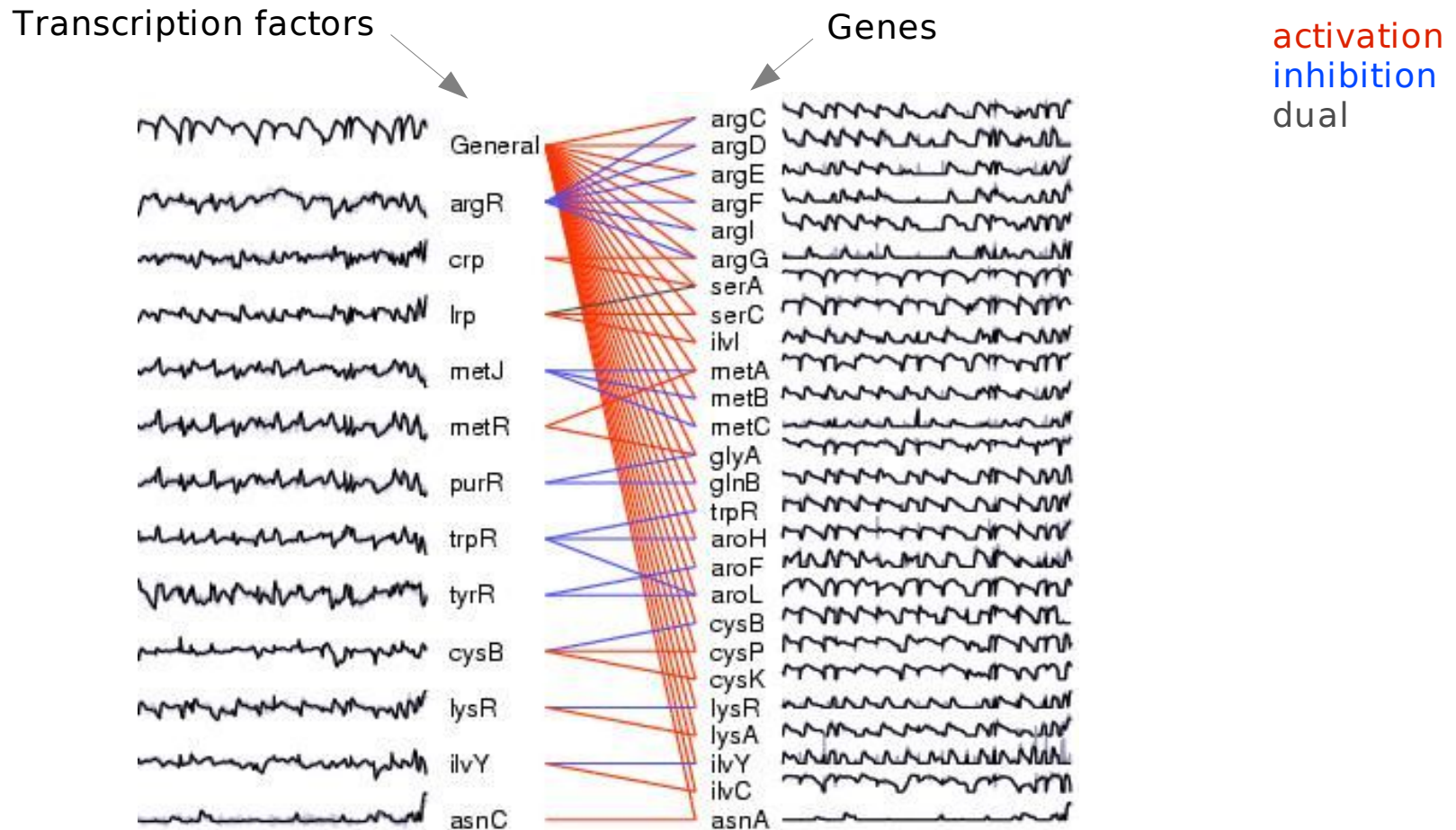
Transcription rates of amino acid biosynthesis genes

Zaslaver et al (2004), Nat Genet 36, 486-491



# Network component analysis

Global modes reflect the activity of transcription factors



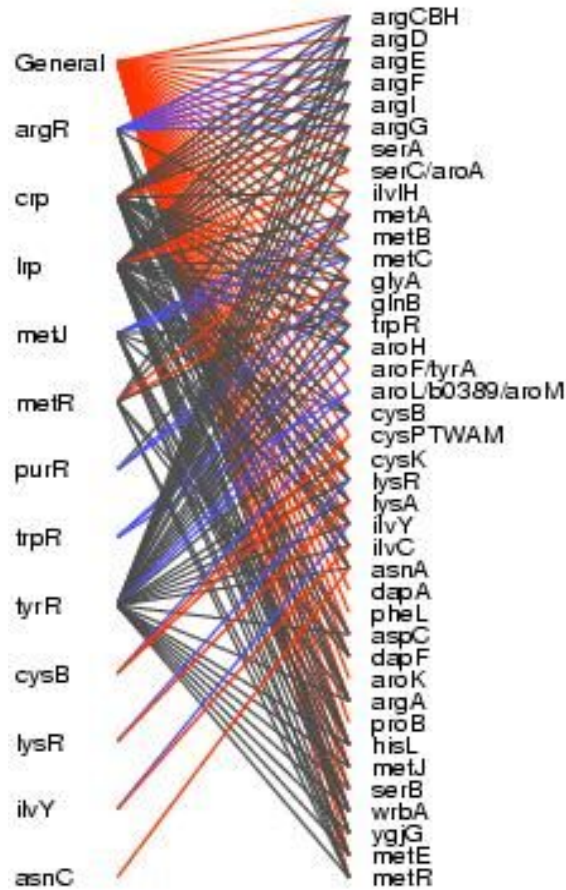
TF activities  
inferred from NCA

Transcription network  
from RegulonDB

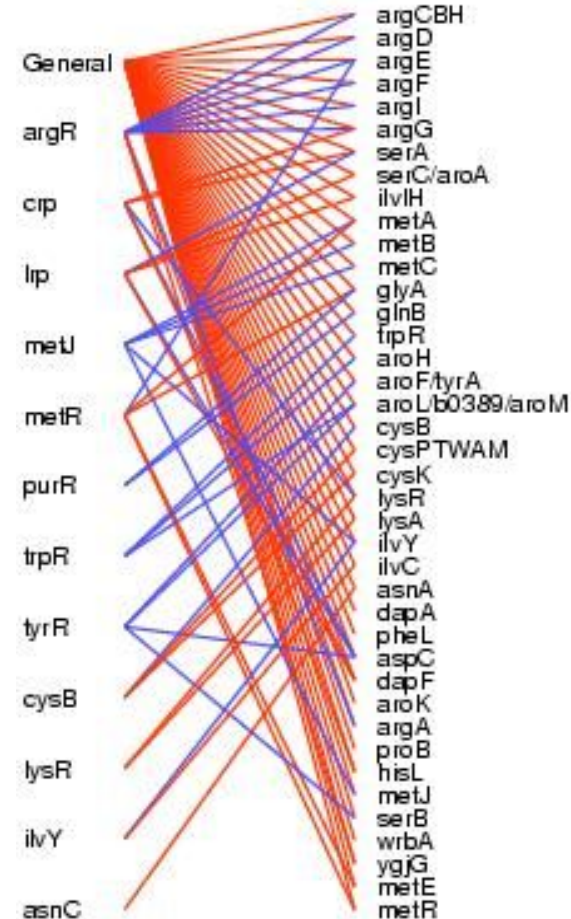
Promoter activities  
Zaslaver et al (2004),  
Nat Genet 36, 486-491

# Inferring new regulatory interactions

Use putative connections and good fit of NCA model



Initial network:  
Known and putative arrows



Selecting of arrows  
supported by expression data

activation  
inhibition  
dual



# Trouble with complex systems

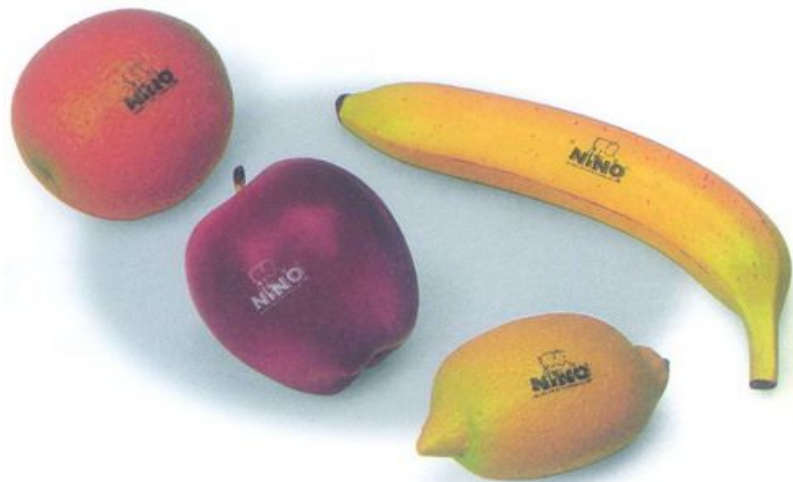
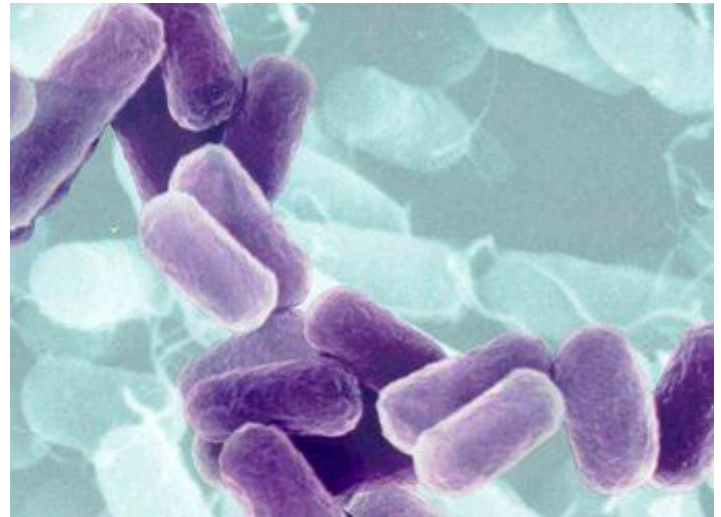
## Things we understand easily

Separate entities

Small numbers

Causal chains

Direct effects



... but living systems are

Continuous

Complex

Dynamic

Adaptive

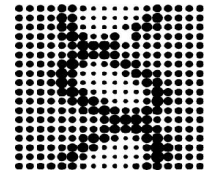
Stochastic

Evolved

# Acknowledgements



Max Planck Institute  
for Molecular Genetics



Edda Klipp  
Simon Borger  
Marvin Schulz  
Jannis Uhlendorf  
Christoph Wierling



EMI-CD - European modelling  
initiative combating complex diseases  
[pybios.molgen.mpg.de/EMICD](http://pybios.molgen.mpg.de/EMICD)



Weizmann Institute of Science



ENFIN  
European Network of Excellence  
[www.enfin.org](http://www.enfin.org)

Uri Alon  
Alon Zaslaver  
Anat Bren  
Shai Kaplan  
Shalev Itzkovitz

# Metabolic response coefficients

## Reaction elasticities

Local response (system clamped)

$$\varepsilon_i^k = \frac{dv_k(\mathbf{x}, \mathbf{p})}{dx_i} \quad \pi_m^k = \frac{dv_k(\mathbf{x}, \mathbf{p})}{dp_m}$$

Change in substrate

Change in enzyme

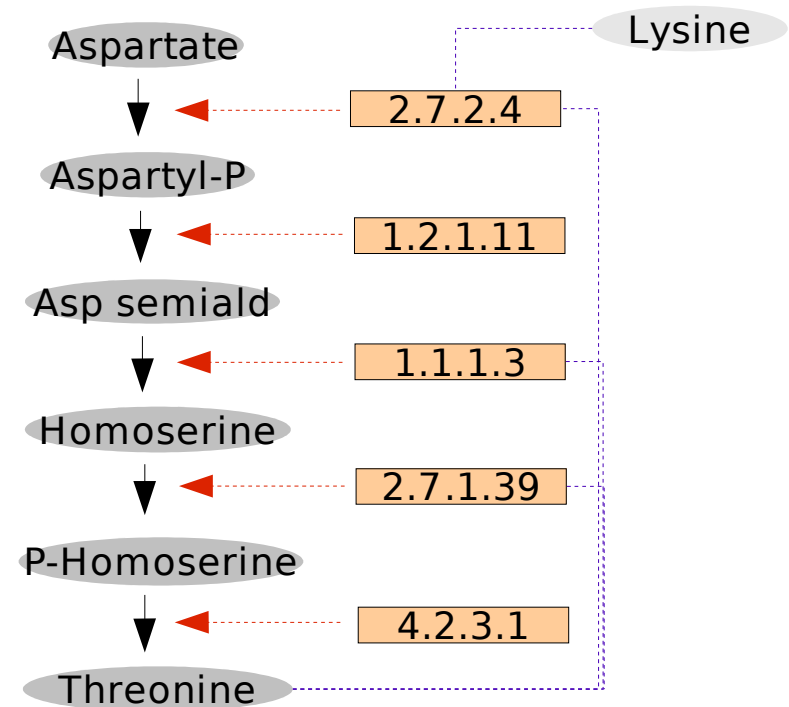
## Response coefficients

Global systemic response

Steady state  
concentrations / fluxes

$$R_{p_m}^{s_i} = \frac{ds_i(\mathbf{p})}{dp_m}$$

$$R_{p_m}^{j_k} = \frac{dj_k(\mathbf{p})}{dp_m}$$

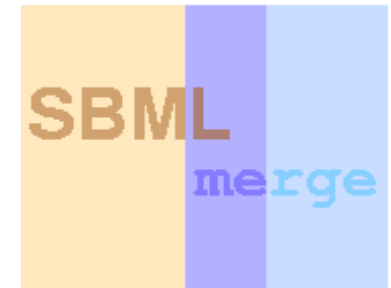


$$R^S = (\mathbf{N}\boldsymbol{\epsilon})^{-1} \mathbf{N}\boldsymbol{\pi}$$

Control coefficients matrix  $C^S$

# SBMLmerge

helps to couple kinetic models



## Annotate the model elements

<http://sysbio.molgen.mpg.de/SBMLmerge/>

String search in data bases  
Automatic recommendations

## Check the model for problems

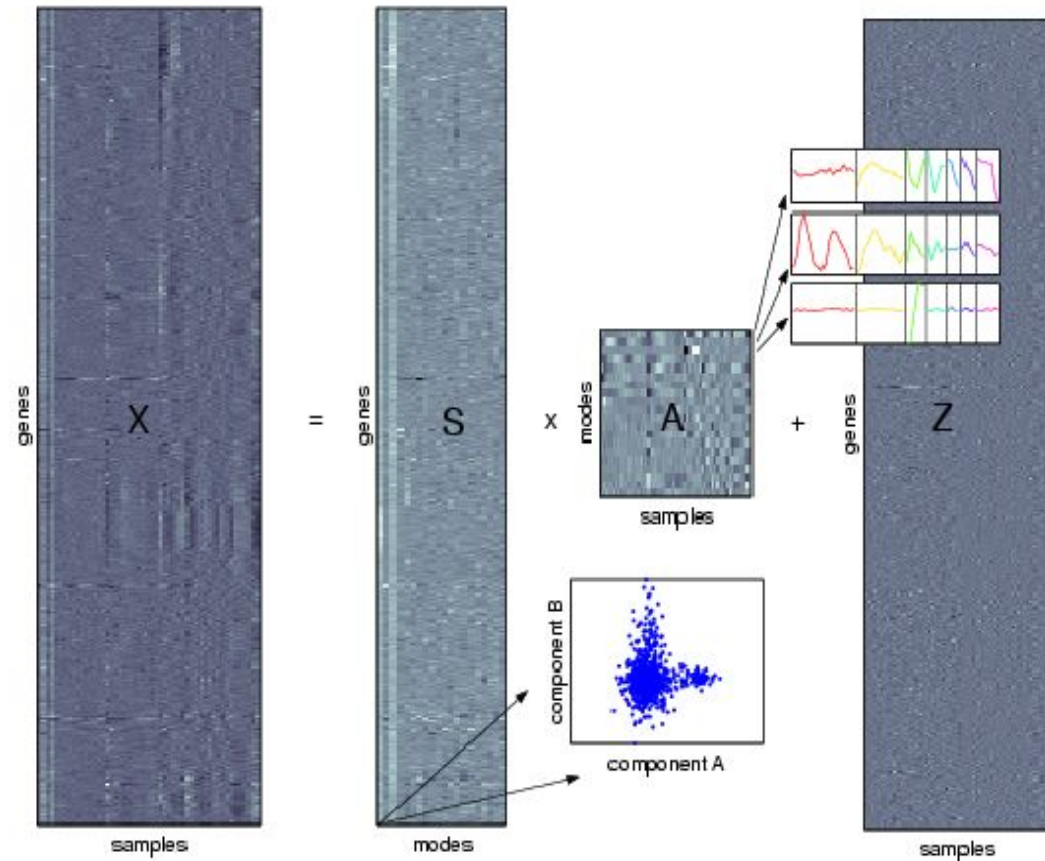
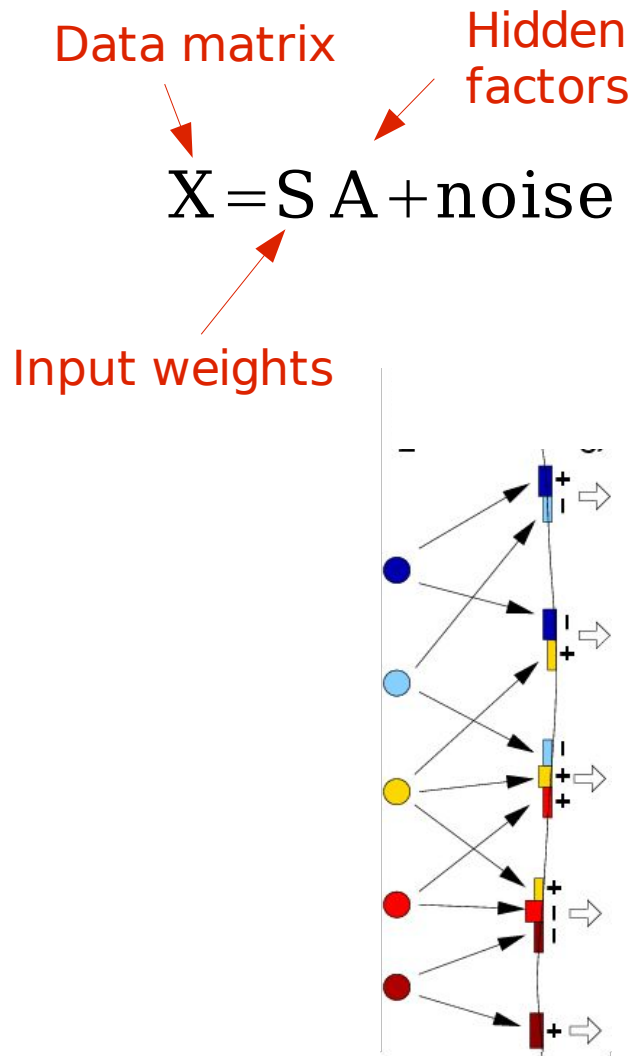
Syntax (low-level validity of SBML code)  
Semantics (annotations and their ontology)  
Mathematics (order of computation,...)  
Physics (thermodynamics, conservation laws, ...)  
Biology (parameter ranges, properties of organism,...)

## Model merging, accounting for

Redundant model elements  
Conflicting information  
Logical cycles

# ICA is a matrix decomposition

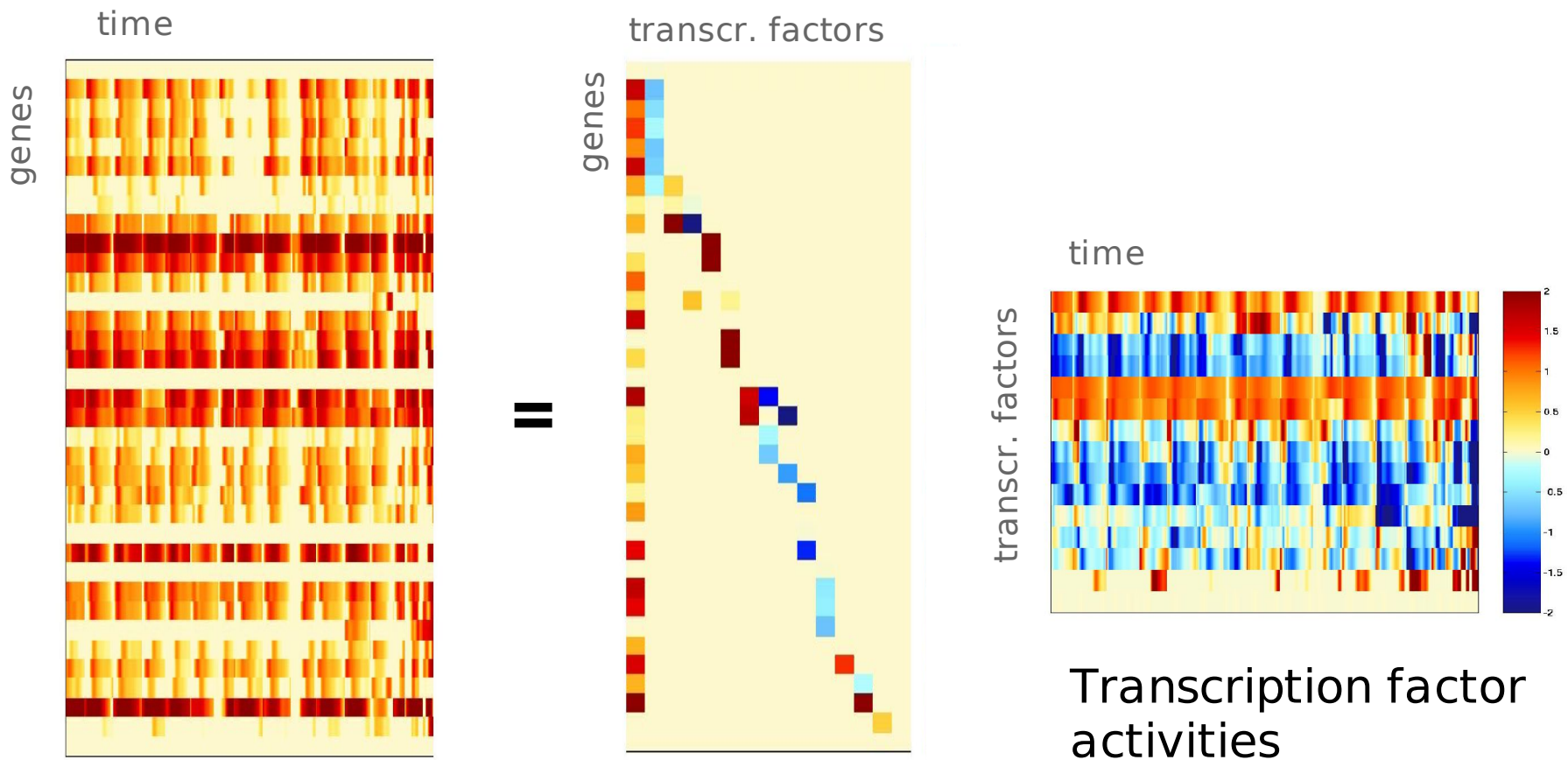
... based on the assumption of statistical independence





# NCA is also based on a matrix decomposition

... and accounts for the transcriptional network

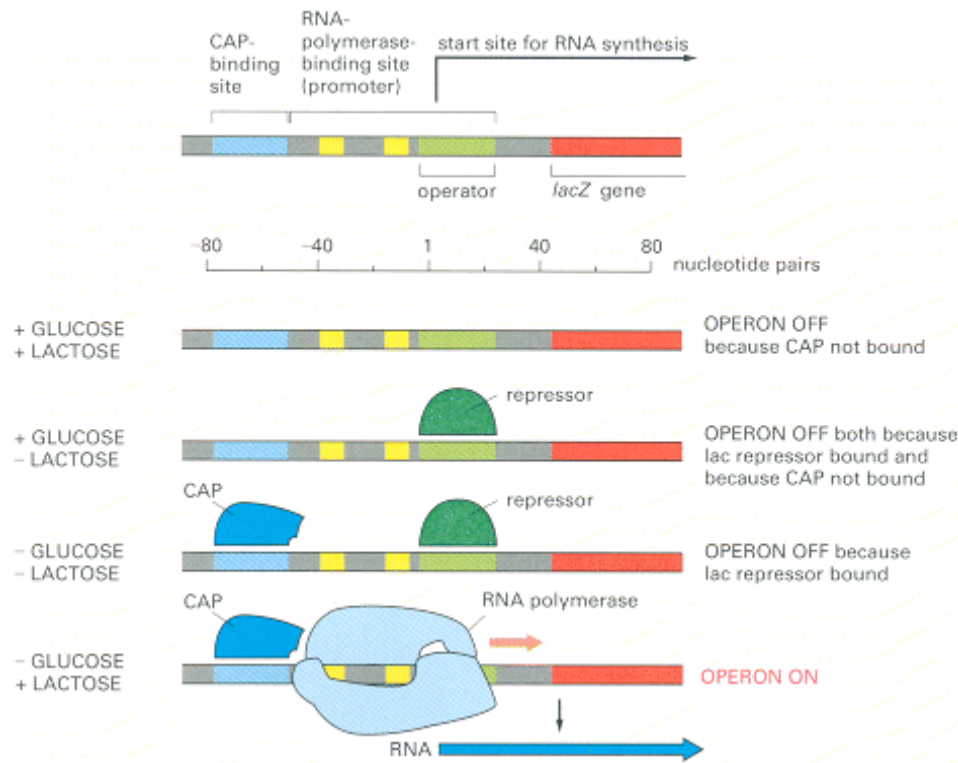


Transcription rates  
experimental

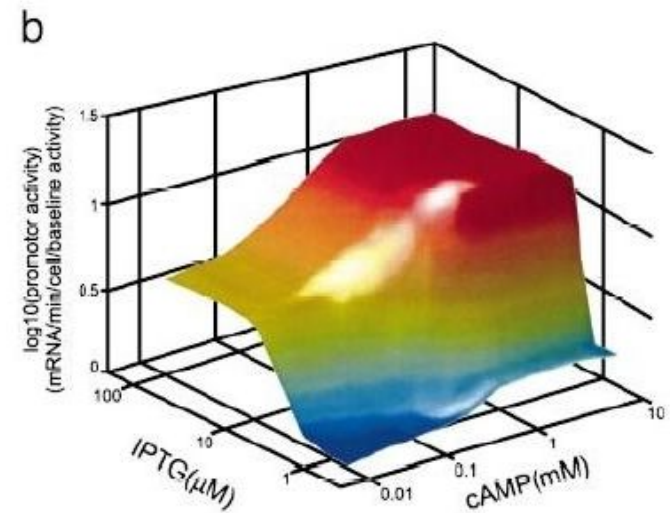
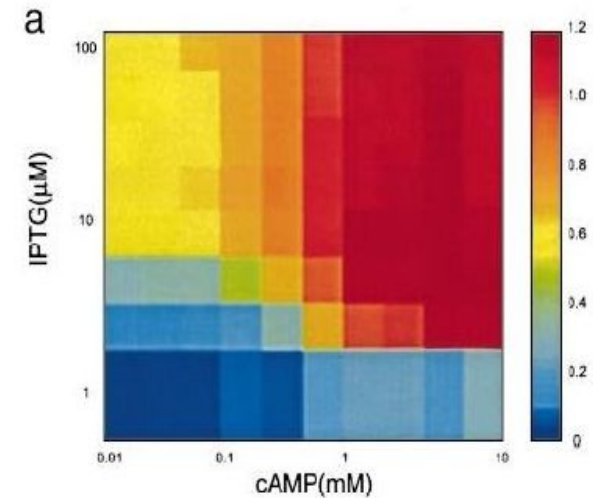
Gene input weights  
connections constrained by network

# Gene input functions

Example: Lac operon in E. Coli



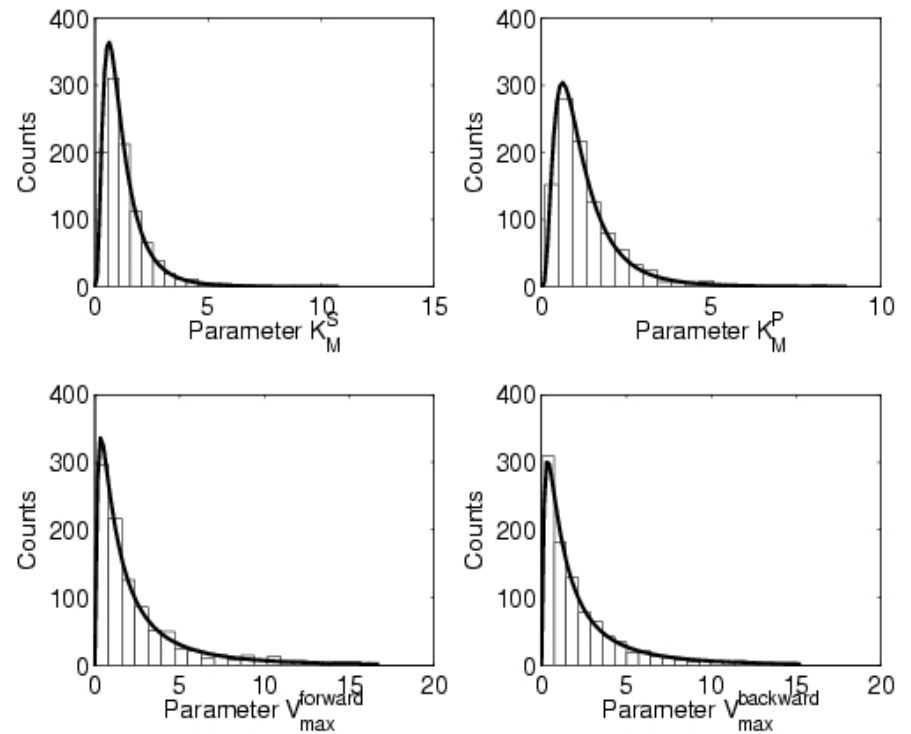
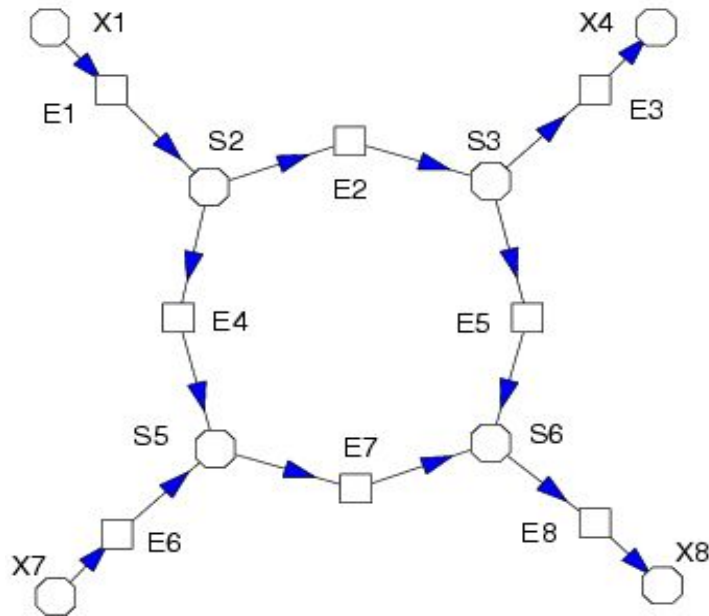
Drawing from [www.ncbi.nlm.nih.gov/books/](http://www.ncbi.nlm.nih.gov/books/)  
Alberts et al, Molecular biology of the cell



Y. Setty, et al (2003). Detailed map of a cis-regulatory input function. PNAS, 100(13):7702-7707

# Fuzzy metabolic networks

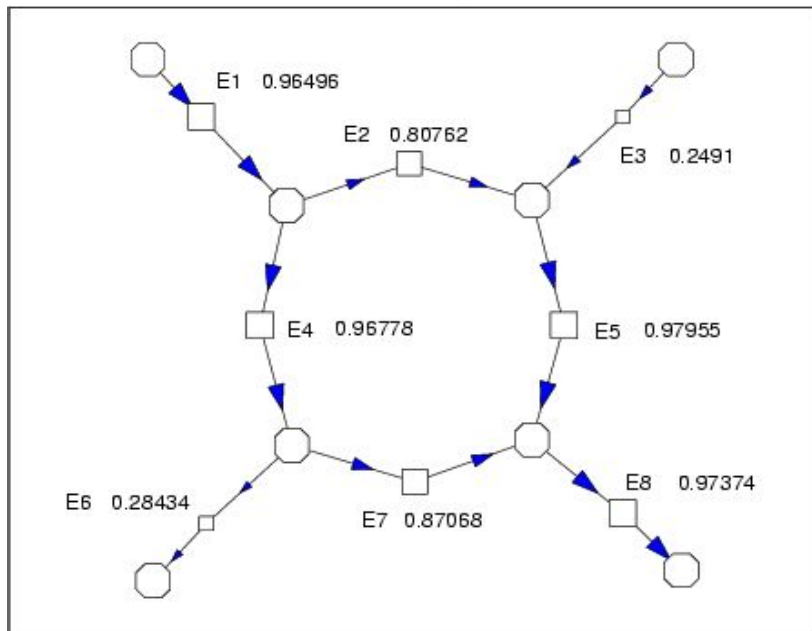
What if parameters are uncertain?



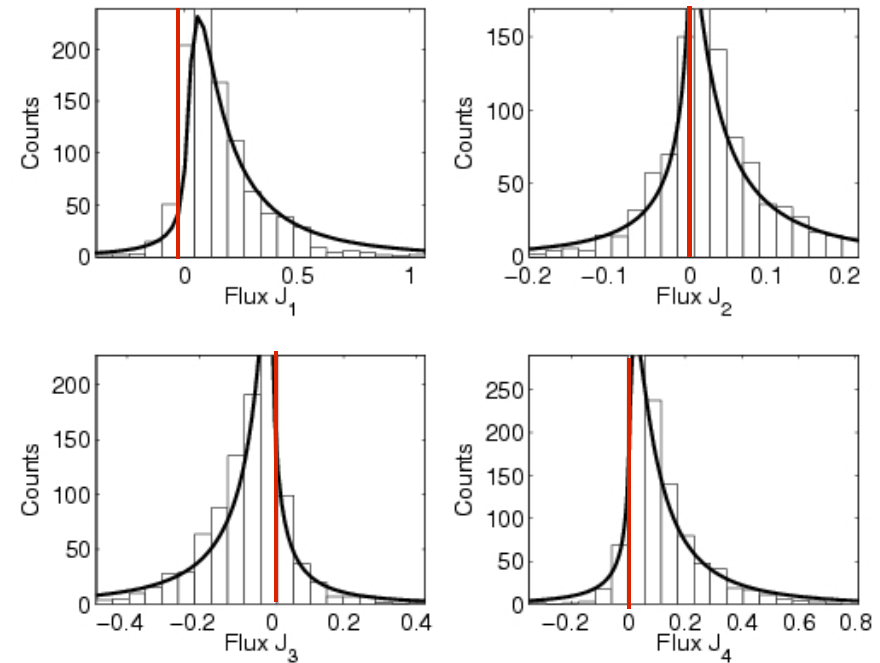
Parameters for reaction E1  
are uncertain (statistical distribution)

# Fuzzy metabolic networks

What if parameters are uncertain?



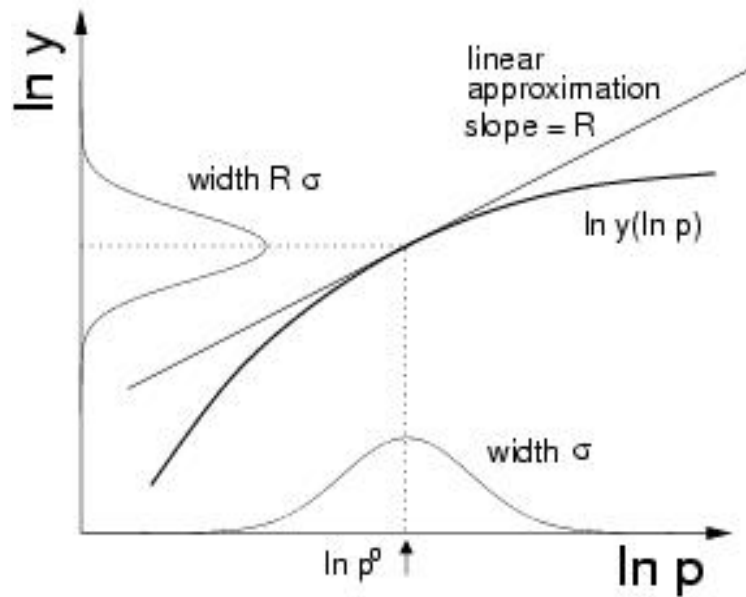
Probabilities of forward flux



Distribution of reaction velocities

# Fuzzy metabolic networks

Studying the effects of parameter variability



Log-normal, correlated  
parameter distributions