Robustness of control in metabolic networks

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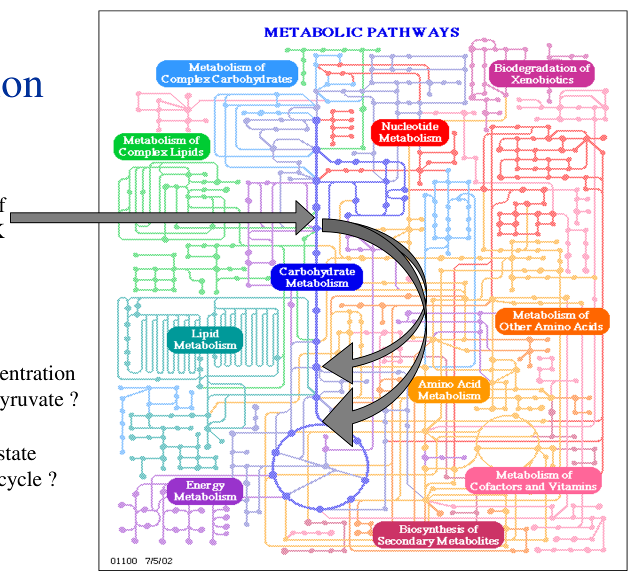
- Introduction
- Definitions
- Simple examples
- Networks
- Outlook

Introduction

Change the activity of one enzyme, e.g. PFK



? Change in the concentration of metabolites, e.g. pyruvate ?

? Change in steady-state fluxes, e.g. in TCA cycle ?

Definition of control coefficients

Metabolic systems are networks; their behaviour relies on the structure of
The network and on the properties of the components.

Two types of coefficients : local and global

Elasticity coefficients | Control coefficients

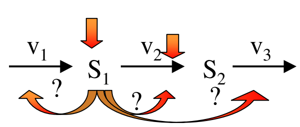
03 June 2003 Robustness of control in metabolic networks 3

Definition of Elasticities

Sensitivity for a rate for change of concentration or parameter
(directly, no steady state, ***local*** property)

1. System of metabolic reactions. $\mathbf{v} = \mathbf{v}(\mathbf{S}(\mathbf{p}),\mathbf{p})$ $\mathbf{S} = \mathbf{S}(\mathbf{p})$
2. **Small** perturbation of a concentration or parameter $S \rightarrow S+\Delta S$

Immediate change in reaction rates due to this perturbation? $v_k \longrightarrow v_k + \Delta v_k$



$$\varepsilon_i^k = \left(\frac{S_i}{v_k} \frac{\Delta v_k}{\Delta S_i} \right)_{\Delta S_i \to 0} = \frac{S_i}{v_k} \frac{\partial v_k}{\partial S_i} = \frac{\partial \ln v_k}{\partial \ln S_i}$$

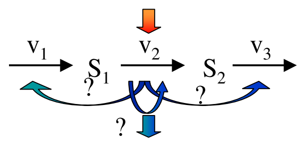
03 June 2003 Robustness of control in metabolic networks 4

Definition of flux control coefficients

Quantitative measure for change of a steady-state variable
(new steady state, dep. on structure of network, global properties)

1. System of metabolic reactions in **steady state**. $J = v(S(p), p)$ $S = S(p)$
2. **Small** perturbation of any reaction
(Addition of enzyme or metabolite,....) $v_k \longrightarrow v_k + \Delta v_k$
3. System goes to new steady state. $J \rightarrow J + \Delta J$ $S \rightarrow S + \Delta S$

Change in steady state-variables (fluxes, concentrations) due to this perturbation?



$$J = v_1 = v_2 = v_3$$

$$C_k^{J_j} = \left(\frac{v_k}{J_j} \frac{\Delta J_j}{\Delta v_k} \right)_{\Delta v_k \to 0} = \frac{v_k}{J_j} \frac{\partial J_j}{\partial v_k} = \frac{\partial \ln J_j}{\partial \ln v_k}$$

Questions, Problems

- Control in certain systems
- How to perturb a system in order to increase
  a certain flux, to decrease a concentration, ... ?

Big scale projects to model metabolism based on
- comprehensive data base information about the network
- non or incomplete kinetic information

How big is the error, if we
- assume wrong kinetics
- take only a small network out of the whole
- neglect „small“ metabolites

?

Calculation of Control Coefficients

Summation theoreme

$$\sum_{k=1}^{r} C_{v_k}^{J_j} = 1$$

Flux control coefficients of a pathway add up to 1.
The Enzymes share the control over the flux.

As matrices: $\mathbf{C}^J \boldsymbol{1} = \boldsymbol{1}$ $\qquad \boldsymbol{1} = \begin{pmatrix} 1 \\ 1 \\ 1 \end{pmatrix}$

Connectivity theoreme

$$\sum_{i=1}^{r} C_{v_i}^{J_m} \varepsilon_{S_j}^{v_i} = 0$$

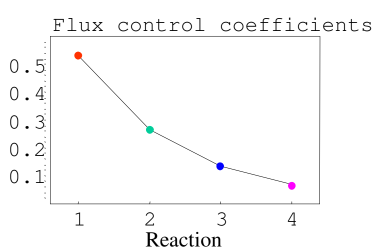
Relation between the set of flux control coefficients and the elasticities

$$\mathbf{C}^J \boldsymbol{\varepsilon} = \mathbf{0}$$

Examples

$$P_1 \overset{v_1}{\longleftrightarrow} S_1 \overset{v_2}{\longleftrightarrow} S_2 \overset{v_3}{\longleftrightarrow} S_3 \overset{v_4}{\longleftrightarrow} P_2$$

$$v_i = E_i\left(k_{+i}S_{i-1} - k_{-i}S_i\right)$$
$$q_i = k_{+i}/k_{-i}$$



Simplest case:

$E_i = 1 \quad P_1 = P_2 = 1$

$k_{+i} = 2, k_{-i} = 1, q_i = 2$

$J = 1$

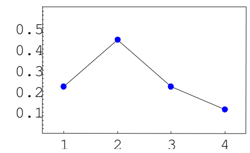
$E_1 \rightarrow E_1 + 1\% \qquad J \rightarrow J + C_1 * 1\% = 1.0056$

Flux increase – how?

Flux control

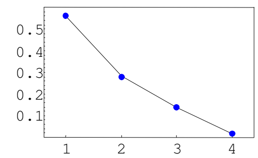
$P_1 \overset{v_1}{\longleftrightarrow} S_1 \overset{v_2}{\longleftrightarrow} S_2 \overset{v_3}{\longleftrightarrow} S_3 \overset{v_4}{\longleftrightarrow} P_2$

$E_1 = 4, E_{2,3,4} = 1$ $J = 1.667$



$P_1 \overset{v_1}{\longleftrightarrow} S_1 \overset{v_2}{\longleftrightarrow} S_2 \overset{v_3}{\longleftrightarrow} S_3 \overset{v_4}{\longleftrightarrow} P_2$

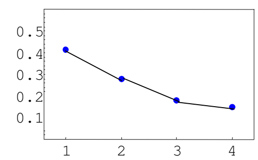
$E_4 = 4, E_{1,2,3} = 1$ $J = 1.06195$



$P_1 \overset{v_1}{\longleftrightarrow} S_1 \overset{v_2}{\longleftrightarrow} S_2 \overset{v_3}{\longleftrightarrow} S_3 \overset{v_4}{\longleftrightarrow} P_2$

$C_i^J = \frac{E_i}{E_{total}}$ $J = 2.00168$

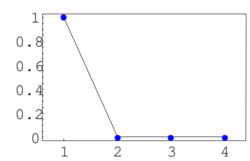
E1→ 2.73367 , E2→ 1.933 , E3→ 1.36684 , E4→ 0.966498



Special Situations

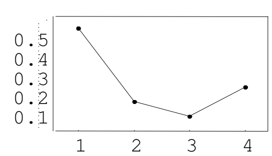
Irreversible reaction

$P_1 \overset{v_1}{\longrightarrow} S_1 \overset{v_2}{\longleftrightarrow} S_2 \overset{v_3}{\longleftrightarrow} S_3 \overset{v_4}{\longleftrightarrow} P_2$



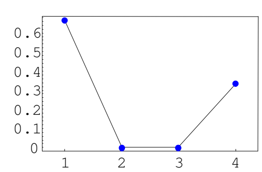
Feedback inhibition

$P_1 \overset{v_1}{\longleftrightarrow} S_1 \overset{v_2}{\longleftrightarrow} S_2 \overset{v_3}{\longleftrightarrow} S_3 \overset{v_4}{\longleftrightarrow} P_2$



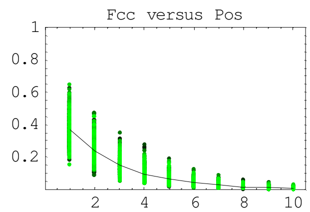
Irreversible reaction with feedback inhibition

$P_1 \overset{v_1}{\longrightarrow} S_1 \overset{v_2}{\longleftrightarrow} S_2 \overset{v_3}{\longleftrightarrow} S_3 \overset{v_4}{\longleftrightarrow} P_2$



Diced Kinetics

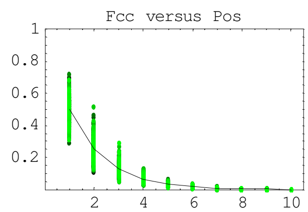
$$P_1 \overset{v_1}{\longleftrightarrow} S_1 \overset{v_2}{\longleftrightarrow} S_2 \overset{v_3}{\longleftrightarrow} \ldots \overset{v_9}{\longleftrightarrow} S_9 \overset{v_{10}}{\longleftrightarrow} P_2$$



Michaelis-Menten Kinetics

$$v_i = \frac{S_{i-1}\dfrac{V^{\rightarrow}_{max,i}}{K_{m,S_{i-1}}} - S_i \dfrac{V^{\leftarrow}_{max,i}}{K_{m,S_i}}}{1+\dfrac{S_{i-1}}{K_{m,S_{i-1}}}+\dfrac{S_i}{K_{m,S_i}}}$$

Kinetic constants: LogNormalDistribution, μ=1,σ=0.25



Linear Kinetics

$$v_i = E_i\left(k_{+i}S_{i-1} - k_{-i}S_i\right)$$

Kinetic constants: LogNormalDistribution, μ=1,σ=0.25

Diced Kinetics

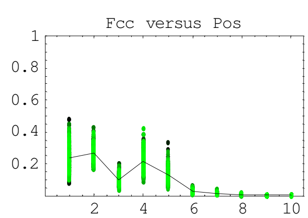
$$P_1 \overset{v_1}{\longleftrightarrow} S_1 \overset{v_2}{\longleftrightarrow} S_2 \overset{v_3}{\longleftrightarrow} \ldots \overset{v_9}{\longleftrightarrow} S_9 \overset{v_{10}}{\longleftrightarrow} P_2$$

Michaelis-Menten Kinetics

StandDev of Means	0.0140337
Mean of StandDev	0.0289852

Linear Kinetics

StandDev of Means	0.0249214
Mean of StandDev	0.0189133



Linear Kinetics with coupling

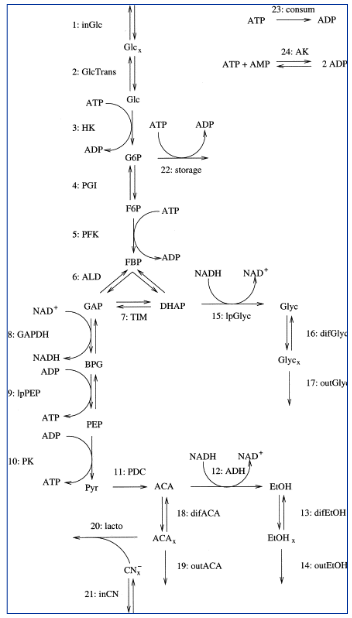
StandDev of Means	0.0112199
Mean of StandDev	0.0225115

Model of Yeast Glycolysis

Hynne R, Dano S, Sorensen PG
Full-scale model of glycolysis in Saccharomyces cerevisiae
BIOPHYS CHEM 94 (1-2): 121-163 DEC 11 2001

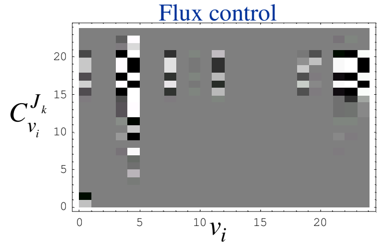
r		Reaction
1	inGlc	$\rightleftharpoons Glc_x$
2	GlcTrans	$Glc_x \rightleftharpoons Glc$
3	HK	$Glc+ATP \rightarrow G6P+ADP$
4	PGI	$G6P \rightleftharpoons F6P$
5	PFK	$F6P+ATP \rightleftharpoons FBP+ADP$
6	ALD	$FBP \rightleftharpoons GAP+DHAP$
7	TIM	$DHAP \rightleftharpoons GAP$
8	GAPDH	$GAP+NAD^+ \rightleftharpoons BPG+NADH$
9	lpPEP	$BPG+ADP \rightleftharpoons PEP+ATP$
10	PK	$PEP+ADP \rightarrow Pyr+ATP$
11	PDC	$Pyr \rightarrow ACA$
12	ADH	$ACA+NADH \rightarrow EtOH+NAD^+$
13	difEtOH	$EtOH \rightleftharpoons EtOH_x$
14	outEtOH	$EtOH_x \rightarrow$
15	lpGlyc	$DHAP+NADH \rightarrow Glyc+NAD^+$
16	difGlyc	$Glyc \rightleftharpoons Glyc_x$
17	outGlyc	$Glyc_x \rightarrow$
18	difACA	$ACA \rightleftharpoons ACA_x$
19	outACA	$ACA_x \rightarrow$
20	lacto	$ACA_x+CN_x^- \rightarrow$
21	inCN	$CN_x^- \rightleftharpoons$
22	storage	$G6P+ATP \rightarrow ADP$
23	consum	$ATP \rightarrow ADP$
24	AK	$ATP+AMP \rightleftharpoons 2\ ADP$

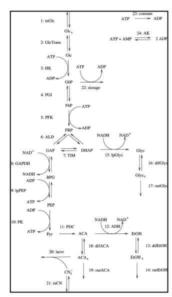
$[NAD^+]+[NADH]$=constant, and $[ATP]+[ADP]+[AMP]$=constant



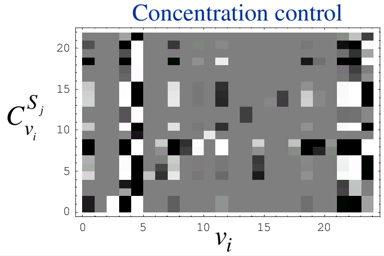
Control Distribution

Flux control

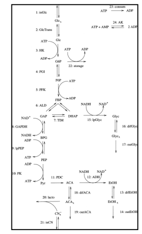




Concentration control

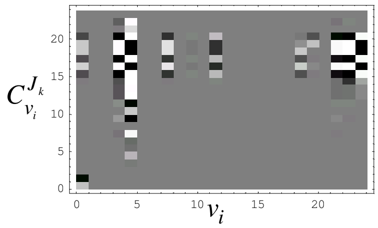


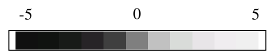
Control coefficients
for most realistic model
(experimentally proven rate laws)



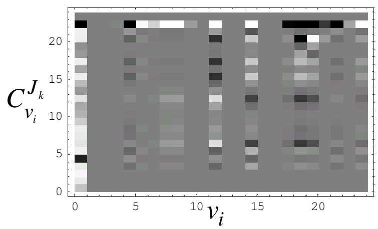
Flux Control, Linear Kinetics

Realistic model

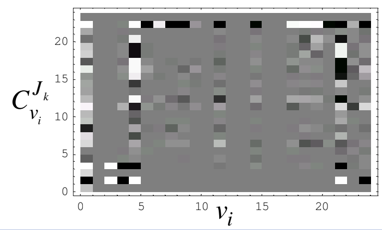


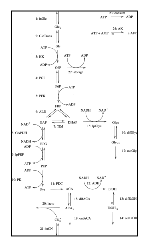


Linear kinetics, all rate constants = 1



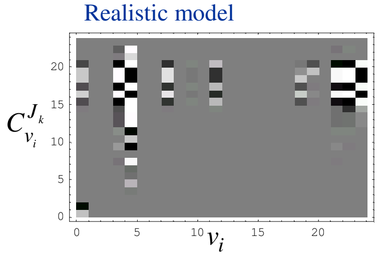
Linear kinetics,
Arbitrary rate constants
Mean of 100 runs

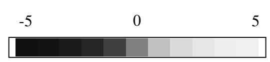




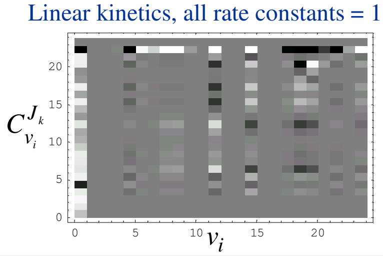
Flux Control, Linear Kinetics

Realistic model

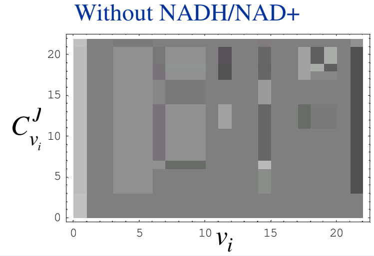




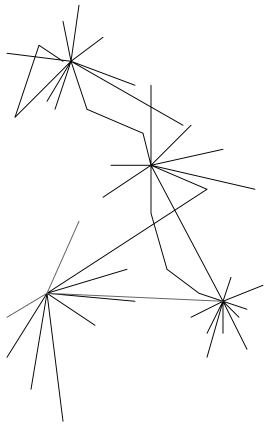
Linear kinetics, all rate constants = 1



Linear kinetics,
All rate constants = 1
Without ATP/ADP/AMP
Without NADH/NAD+



Big Networks



First results:
starting at neighbouring reactions and including further reactions iteratively leads soon to a convergence of control coefficients
→ Control relies mainly on conditions in sub-networks.

Measure for Robustness of Control

Mean of Standard deviation of Control coefficients

Number of Control coefficients keeping their sign upon change of kinetics

For a fixed distribution of kinetic constants

Or compared to the total parameter variation

$$T = \sum_{\mathbf{param.}} \left| \mathbf{log}_{10} \frac{p_i}{p_{i,\,ref}} \right|$$

Conclusions

The real structure of the network matters
- regulatory couplings
- „small molecules“
- (ir-)reversibility

Knowledge of appropriate kinetic laws is important
- dicing may help a bit