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

Definition of Elasticities

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

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

Immediate change in reaction rates due to this perturbation:

\[
\frac{\Delta v_k}{v_k} = \frac{\Delta S_i}{S_i} \quad \text{for} \quad i = 1, 2, \ldots
\]

\[
e_i^k = \left( \frac{S_i}{v_k} \right) \frac{\Delta v_k}{\Delta S_i} \quad \text{for} \quad i = 1, 2, \ldots
\]

\[
e_i^k = \frac{S_i}{v_k} \frac{\partial v_k}{\partial S_i} = \left( \frac{\partial v_k}{\partial S_i} \right)
\]

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**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, ....)
   \[ v_k \rightarrow v_k + \Delta v_k \]
3. System goes to new steady state. \( J + \Delta J \) \( S - \delta + \Delta S \)

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

\[
\frac{C_i'}{C_i} = \left( \frac{\Delta J}{J} \right)_{\Delta v_k = 0} = \frac{\Delta J}{J} \frac{\partial J}{\partial v_k} = \frac{\partial \ln J}{\partial v_k}
\]

**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 theorem**

\[ \sum_{k=1}^{r} C^j_{v_k} = 1 \]

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

As matrices:

\[ C^j J = I \quad \begin{bmatrix} 1 \\ 0 \\ 1 \end{bmatrix} \]

**Connectivity theorem**

\[ \sum_{i=1}^{r} C^j_{v_i} \epsilon_{S_j} = 0 \]

Relation between the set of flux control coefficients and the elasticities

\[ C^j g = 0 \]

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**Examples**

\[ P_1 \xrightarrow{v_1} S_1 \xrightarrow{v_2} S_2 \xrightarrow{v_3} S_3 \xrightarrow{v_4} P_2 \]

\[ v_i = E_i (k_{s_i} - k_{r_i}) \]

\[ q_i = k_{s_i} / k_{r_i} \]

**Simplest case:**

\[ E_1 = 1 \quad P_1 = P_2 = 1 \]

\[ k_{s_i} = 2, k_{r_i} = 1, q_i = 2 \]

\[ J = 1 \]

\[ E_1 \rightarrow E_1 + 1\% \quad J \rightarrow J + C_1 * 1\% = 1.0056 \]
Flux increase – how?

\[ P_1 \xrightarrow{v_1} S_1 \xrightarrow{v_2} S_2 \xrightarrow{v_3} S_3 \xrightarrow{v_4} P_2 \]

\[ E_1 = 4, E_{2,3,4} = 1 \quad J = 1.667 \]

\[ P_1 \xrightarrow{v_1} S_1 \xrightarrow{v_2} S_2 \xrightarrow{v_3} S_3 \xrightarrow{v_4} P_2 \]

\[ E_4 = 4, E_{1,2,3} = 1 \quad J = 1.06195 \]

\[ P_1 \xrightarrow{v_1} \begin{array}{c} \uparrow \\ S_1 \end{array} \xrightarrow{v_2} \begin{array}{c} \uparrow \\ S_2 \end{array} \xrightarrow{v_3} \begin{array}{c} \uparrow \\ S_3 \end{array} \xrightarrow{v_4} P_2 \]

\[ C'_i = \frac{v_i}{E_{\text{total}}} \quad J = 2.00168 \]

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Special Situations

Irreversible reaction

\[ P_1 \xrightarrow{v_1} S_1 \xrightarrow{v_2} S_2 \xrightarrow{v_3} S_3 \xrightarrow{v_4} P_2 \]

Feedback inhibition

\[ P_1 \xrightarrow{v_1} \begin{array}{c} \uparrow \\ S_1 \end{array} \xrightarrow{v_2} \begin{array}{c} \uparrow \\ S_2 \end{array} \xrightarrow{v_3} \begin{array}{c} \uparrow \\ S_3 \end{array} \xrightarrow{v_4} P_2 \]

Irreversible reaction with feedback inhibition

\[ P_1 \xrightarrow{v_1} \begin{array}{c} \uparrow \\ S_1 \end{array} \xrightarrow{v_2} \begin{array}{c} \uparrow \\ S_2 \end{array} \xrightarrow{v_3} \begin{array}{c} \uparrow \\ S_3 \end{array} \xrightarrow{v_4} P_2 \]
**Diced Kinetics**

\[ P_1 \xrightarrow{v_1} S_1 \xleftrightarrow{v_1'} S_2 \xrightarrow{v_2} \ldots \xrightarrow{v_9} S_9 \xleftrightarrow{v_9'} P_2 \]

**Michaelis-Menten Kinetics**

\[ v_i = \frac{V_{\text{max},i} S_i}{K_{\text{m},i} + S_i} \]

Kinetic constants: LogNormalDistribution, \( \mu = 1, \sigma = 0.25 \)

**Linear Kinetics**

\[ v_i = E_i(k_{\text{in}}, S_{\text{pos}}, S_i) \]

Kinetic constants: LogNormalDistribution, \( \mu = 1, \sigma = 0.25 \)

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**Diced Kinetics**

\[ P_1 \xrightarrow{v_1} S_1 \xleftrightarrow{v_1'} S_2 \xrightarrow{v_2} \ldots \xrightarrow{v_9} S_9 \xleftrightarrow{v_9'} P_2 \]

**Michaelis-Menten Kinetics**

\[ v_i = \frac{V_{\text{max},i} S_i}{K_{\text{m},i} + S_i} \]

Kinetic constants: LogNormalDistribution

\[ \text{StandDev of Means} = 0.0140337 \]
\[ \text{Mean of StandDev} = 0.0289852 \]

**Linear Kinetics**

\[ v_i = E_i(k_{\text{in}}, S_{\text{pos}}, S_i) \]

Kinetic constants: LogNormalDistribution

\[ \text{StandDev of Means} = 0.0249214 \]
\[ \text{Mean of StandDev} = 0.0189133 \]

**Linear Kinetics with coupling**

\[ \text{StandDev of Means} = 0.0112199 \]
\[ \text{Mean of StandDev} = 0.0225115 \]
**Model of Yeast Glycolysis**

Hyeon R. Dana, S. Sorensen PG

Full-scale model of glycolysis in Sacccharomyces cerevisiae

**BIOPHYS CHEM** 94 (1-2): 121-163 DEC 11 2001

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<tr>
<th>Flux control</th>
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Control coefficients for most realistic model (experimentally proven rate laws)
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

\[
T = \sum_{\text{param.}} \log_{10} \left( \frac{p_i}{p_{i,\text{ref}}} \right)
\]
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