Dynamic behavior determines design strategies of regulation in metabolic networks

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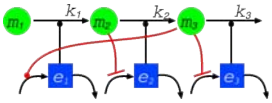
Enzyme activities are tightly regulated

Our goal is to uncover design principles of regulation of enzyme activity that optimize an objective function in a simple metabolic network. In metabolic networks enzyme activity is tightly regulated to adjust metabolite dynamics according to demands on the metabolism.

1

$$V_{max} = k_{kat} e$$



Enzyme activity is defined as a product of the enzyme catalytic rate constant and its total concentration. We examine the effect of the latter by transcriptional regulation. The basis is a simple metabolic network with three metabolites and three enzymes. Metabolites can activate (red line with circle) or inhibit (red line with bar) enzyme expression.

2

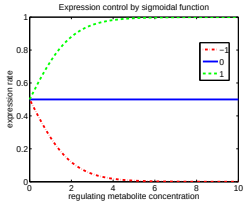
$$\frac{dm_2}{dt} = k_1 e_1 m_1 - k_2 e_2 m_2$$
$$\frac{de_2}{dt} = P(m, W) - k_d e_2$$

Rate equations for concentrations of metabolite M_2 and enzyme E_2. Metabolic reaction rate constants (k_1 to k_3) are randomly distributed on integers in the interval [1,10] for 50 independent combinations (*Metabolic Individuals*). The constant k_d is set to 1.

3

$$P(m, W) = \frac{1}{1 + \exp\left(-\sum_j W_j m_j\right)}$$

The function P controls synthesis of enzymes. It is a sigmoidal function with input of regulation quality (W_j:activating: +1, inhibiting: -1) and the metabolite concentration j that regulates. The output is the expression rate in an interval [0,1]. In case of no regulation the expression rate is 0.5.



Quantification of effectiveness for all possible regulation strategies

4

$$W = \begin{pmatrix} 0 & 0 & 1 \\ 0 & -1 & 0 \\ 0 & 0 & -1 \end{pmatrix} \Rightarrow \begin{array}{c} \\ e_1 \\ e_2 \\ e_3 \end{array} \begin{array}{c} \begin{array}{ccc} m_1 & m_2 & m_3 \end{array} \\ \begin{pmatrix} 1 & 4 & 7 \\ 2 & 5 & 8 \\ 3 & 6 & 9 \end{pmatrix} \end{array}$$

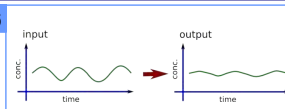
Matrix W contains the regulation qualities of metabolites to enzymes. In the example above metabolite m_2 inhibits its degradation via e_2 while m_3 activates e_1 and inhibits e_3, coded with the ordinal numbers 5, 7 and 9 (cf. network in Box. 1).

5

The number of non-zero elements in the regulation matrix W indicates the number of regulations. We examine conditions with one, two and three regulations (non-zero elements in W). Based on a fitness objective the effectiveness of every regulation is rated for any of the 50 Metabolic Individuals (cf. Box 2).

# of combinations 1 regulation:	18
# of combinations 2 regulations:	144
# of combinations 3 regulations:	672

6



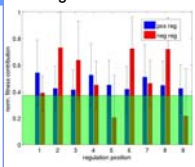
$$f = \frac{1}{k_{big} + \mathrm{var}(m_3)} \cdot \frac{\mathrm{mean}(m_3)}{\mu}$$

$$\mathrm{var}(m_3) = \mathrm{variance}[m_3(t_{\frac{final}{2}}) : m_3(t_{final})]$$
$$\mathrm{mean}(m_3) = \mathrm{mean}[m_3(t_{\frac{final}{2}}) : m_3(t_{final})]$$

Among biological significant fitness functions we implemented the reduction of variation. We set m_1 to oscillate as a sinusoidal and tested m_3 of its capacity to reduce this oscillation. The first part of the fitness function penalizes an increase in variation. The second part in the function penalizes deviation from the m_3 concentration in a non-regulated network (μ).

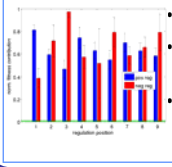
Different network dynamics cause different regulations distribution

7 One regulation



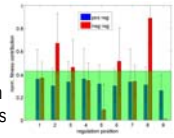
Bar plot of the regulation ordinals (cf. Box 4) and their fitness based on the equation in Box 6.
Green line indicates the limit for beneficial regulations, representing the sum of mean and standard deviation (s.d.) of a non-regulated network.
Most regulations are beneficial, albeit with a high s.d. To reduce s.d. we sub-divided the population into 13 individuals with and without accumulation in m_3 (cf. Box 1).

Low m_3 accumulation



- Reduced s.d.
- All regulations are highly beneficial
- Blue bars decrease in rows of three, red bars increase

High m_3 accumulation

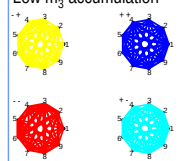


- High s.d.
- Few regulations are beneficial
- No obvious symmetries of regulations

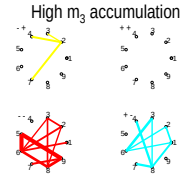
8 Two regulations

We use the regulation roses to visualize two regulations. Lines connect the ordinal numbers of regulation whose thickness represents fitness.

Low m_3 accumulation



High m_3 accumulation

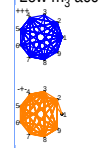


Low m_3 accumulation networks have comparable fitness values for all regulations, but to clearly distinguishable regulation strategies in m_3. For two regulations dynamic properties of the networks have higher impact on fitness than regulation quality.

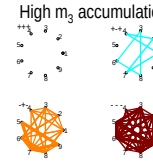
9 Three regulations

The fitness for three regulation interactions is represented by the thickness of triangles.

Low m_3 accumulation



High m_3 accumulation



Networks with high accumulation show that contrasting regulations also have contrasting effects on the fitness. Many triple negative regulations can be used, while no triple positive regulation is >.25 of the highest fitness. Regulation -5, +7, -9 (orange line, cf. Box 1, 5) for high m_3 is particularly beneficial.

Results/Conclusions

We explored regulation distributions of simple metabolic networks (cf. Box 1) based on their capacity to reduce oscillation (cf. Box 6) and conclusions are restricted to this condition.

Dynamic properties and flow rate determine the distribution of optimal regulations:

• Networks that do not accumulate the tested metabolite m_3 have a wide choice of optimal regulations. These networks are characterized by low k_1 and high k_3 values. Reducing the inflow of oscillating substrate to the system allows for more regulation.

Regulation interactions have different effects compared to the individual regulation effects:

• The triple regulation interaction coded by ordinal numbers [-5, +7, -9] is highly beneficial (cf. Box 9). Each regulation in solitude is detrimental for the fitness (cf. Box 7).

Contrasting regulation schemes must not have contrasting fitness effects:

• For networks that accumulate the tested metabolite m_3 the interaction of two purely inhibitory regulations is beneficial, while the interaction of two activating regulations is detrimental (cf. Box 8). However, networks without m_3 accumulation show no substantial differences in regulation efficiencies for positive and negative regulation interactions.

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