Metabolism and gene regulation

Gene products/enzymes catalyse reactions.
Genes are regulated by gene and reaction products.

Metabolism adapts to changing environments.
Even in constant environments, metabolism exhibits changes in enzyme activity.
Significant metabolic alterations during cell cycle.


Working hypothesis

Switching between pathways may improve overall efficiency:

The output is produced by a single flux mode, using all reactions.
Two consecutive flux modes produce the output with higher flux rates.

When is this possible?

Assume metabolic network with internal metabolites $M_\text{in}$ and output metabolites $M_\text{out}$, for which there is a demand $\Gamma$.
A flux mode $v$ which is executed for some time $\tau \geq 0$ satisfies the demand if $\tau \cdot S^*v \geq \Gamma$.
Two flux modes $v^1, v^2$ which are executed consecutively for time $\tau_1$ resp. $\tau_2$ satisfy the demand if $\tau_1 \cdot S^*v^1 + \tau_2 \cdot S^*v^2 \geq \Gamma$.
Can we be more efficient with two flux modes $v^1, v^2$ than with one flux mode $v$?
In an FBA context, this is not possible, since we may always choose $\nu = \frac{\tau_1}{\tau_1 + \tau_2} v^1 + \frac{\tau_2}{\tau_1 + \tau_2} v^2$, which has the same efficiency $\tau = \tau_1 + \tau_2$. 
Assume $0 \leq v \leq \frac{ub}{|supp(v)|}$, i.e., flux bound depends on number of active reactions.

To satisfy demand, need $1.25 \cdot v^1 + 1.25 \cdot v^2$, i.e., $\tau = 2.5$.

Basic assumption: Total amount of protein in the cell is limited.
Sharing available enzymes

- Synthesis and degradation of $j$-th enzyme:
  \[ \frac{dE_j}{dt} = g_j k_s j A - k_d j E_j \]
  where $A$ is the total mass of free amino acids.
- Steady-state condition:
  \[ E_j = g_j A \eta_j \]
  with $\eta_j = \frac{k_s j}{k_d j}$.
- Assume fixed total mass of amino acids
  \[ A_{tot} = A + \sum E_i \gamma_i = A + \sum (g_i A \eta_i) \gamma_i = A(1 + \sum g_i \gamma_i \eta_i) \]
  where $\gamma_i$ is the molecular mass of the $i$-th enzyme.
- Resulting upper bound:
  \[ v_j \leq k c_j \cdot E_j = k c_j \cdot A_{tot} \frac{g_j \eta_j}{1 + \sum g_i \gamma_i \eta_i} \]

Non-linear mixed 0-1 optimisation problem

\[ \min \sum_{k=1}^l \tau_k \]
\[ S^# v^k = 0, \quad \sum_{k=1}^l \tau_k S^* v^k \geq \Gamma, \]
\[ lb_j \leq v_j^k \leq k c_j \cdot A_{tot} \frac{g_j \eta_j}{1 + \sum g_i \gamma_i \eta_i}; \]
\[ l \in \mathbb{N}, k = 1, \ldots, l, j = 1, \ldots, n, \]
\[ \tau_k \in \mathbb{R}_{\geq 0}, v^k \in \mathbb{R}^n, g^k \in \{0,1\}^n. \]
\[ \text{can be reformulated as mixed 0-1 quadratic program (MIQP).} \]

Optimizing cellular output

- Internal metabolites $M^#$, output metabolites $M^*$, all reactions irreversible.
- Assume cell has to produce a certain amount $\Gamma$ of output metabolites $M^*$.
- Allow using up to $l$ flux modes $v^1, \ldots, v^l$ in $l$ consecutive time intervals of length $\tau_1, \ldots, \tau_l$.
- Output in $k$-th time interval: $\tau_k \cdot S^* v^k$
- Goal: Minimize the total time $\tau_1 + \cdots + \tau_l$ needed to produce $\Gamma$.
- Lower bounds $lb \geq 0$ (minimum activity of certain reactions).

Modeling gene expression levels

- $g \in [0,1]^n$: fine tuning of genes
  (similar to FBA with Molecular Crowding, cf. Beg et al. 2007)
  $\Rightarrow$ feasible region is convex
  $\Rightarrow$ no improvement possible through switching
- $g \in \{0,1\}^n$: genes switched on or off individually.
- $g \in U \subset \{0,1\}^n$: genes switched on or off in functional groups,
  $\Rightarrow$ biologically more meaningful
  (e.g. common transcription factors)
  $\Rightarrow$ may use MinModes (Hoffmann et al. 2006)
Simplistic example

- Improvement by switching depends on parameter values.
- Random sampling gives improvement in 83% of the cases.
- Higher improvement if more protein is spent downstream.

Optimal MinMode solutions

<table>
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<tr>
<th>Sub</th>
<th>( \Sigma )</th>
<th>( t_1 )</th>
<th>( t_2 )</th>
<th>( t_3 )</th>
<th>( t_4 )</th>
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<td>2.362h</td>
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<td>4.792h</td>
<td>2.214h</td>
<td>0.098h</td>
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<td>26 (8/8/10)</td>
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<tr>
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<td>1.386h</td>
<td>0.121h</td>
<td>14 (4/3/7)</td>
<td>32,32,35,36</td>
</tr>
</tbody>
</table>

First MinMode solution
Results depend on the parameter values, but the benefit of switching is persistent.

- No improvement if feasible region is convex.
- MinMode solutions ($U \subseteq \{0, 1\}^n$) biologically more realistic.
- Number of pathways in an optimal solution can be bound by number of output metabolites ($l \leq |M^*|$).
- MIQP remains difficult to solve.