10. Sequential metabolic phases

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


Working hypothesis

Palinkas/Bulik/Bockmayr/Holzhütter 15

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 $M^\#$ and output metabolites $M^*$, for which there is a demand $\Gamma$.
- A flux mode $\nu$ which is executed for some time $\tau \geq 0$ satisfies the demand if $\tau \cdot S^* \nu \geq \Gamma$.
- Two flux modes $\nu_1, \nu_2$ which are executed consecutively for time $\tau_1$ resp. $\tau_2$ satisfy the demand if $\tau_1 \cdot S^* \nu_1 + \tau_2 \cdot S^* \nu_2 \geq \Gamma$.
- Can we be more efficient with two flux modes $\nu_1, \nu_2$ than with one flux mode $\nu$?
- In an FBA context, this is not possible, since we may always choose $\nu = \frac{\tau_1}{\tau_1 + \tau_2} \nu_1 + \frac{\tau_2}{\tau_1 + \tau_2} \nu_2$, which has the same efficiency $\tau = \tau_1 + \tau_2$.

Illustrating the principle

Assume $0 \leq \nu \leq ub / |supp(\nu)|$, i.e., flux bound depends on number of active reactions.

demand of metabolite production: 10 10
Illustrating the principle

Assume flux bounds $0 \leq v \leq \frac{ub}{|supp(v)|}$, here $ub = 40$.

\[
\frac{ub}{|supp(v^1)|} = \frac{40}{5} = 8 \\
\frac{ub}{|supp(v^2)|} = \frac{40}{5} = 8
\]

output: 8 output: 8

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

A. Bockmayr, Metabolic Networks, 7 July 2016

Illustrating the principle

Assume flux bounds $0 \leq v \leq \frac{ub}{|supp(v)|}$, here $ub = 40$.

\[
\frac{ub}{|supp(v^3)|} = \frac{40}{8} = 5
\]

output: 2.5 output: 2.5

To satisfy demand, need $4 \cdot v^3$, i.e., $\tau = 4$.

A. Bockmayr, Metabolic Networks, 7 July 2016

Modeling approach

- Synthesis and degradation of $j$-th enzyme:
  \[
  \frac{dE_j}{dt} = g_j ks_j A - kd_j E_j,
  \]
  where $A$ is the total mass of free amino acids.

- Steady-state condition:
  \[
  E_j = g_j A \eta_j, \text{ with } \eta_j = ks_j / kd_j.
  \]

- Assume fixed total mass of amino acids
  \[
  A_{tot} = A + \sum E_i \gamma_i = A(1 + \sum_i g_i \gamma_i \eta_i)
  \]
  where $\gamma_i$ is the molecular mass of the $i$-th enzyme.

- Resulting upper bound:
  \[
  v_j \leq kc_j \cdot E_j = kc_j \cdot A_{tot} \frac{g_j \eta_j}{1 + \sum_i g_i \gamma_i \eta_i}
  \]

A. Bockmayr, Metabolic Networks, 7 July 2016
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).

Non-linear mixed 0-1 optimisation problem

$$\min \sum_{k=1}^l \tau_k$$
$$S^# v^k = 0,$$
$$\sum_{k=1}^l \tau_k S^* v^k \geq \Gamma,$$
$$lb_j \leq v^k_j \leq kc_j \cdot \text{Atot} \cdot \frac{g^j_i \eta^j_i}{1 + \sum_i g^j_i \eta^j_i},$$
$$l \in \mathbb{N}, k = 1, \ldots, l, j = 1, \ldots, n,$$
$$\tau_k \in \mathbb{R}_{\geq 0}, v^k \in \mathbb{R}^n, g^k \in \{0, 1\}^n.$$

\(\Rightarrow\) can be reformulated as mixed 0-1 quadratic program (MIQP).

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)

Toy 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.
Biomass in central carbon metabolism

Optimal MinMode solutions

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First MinMode solution

Second MinMode solution
Discussion

- 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.