Designing optimal cell factories: integer programming couples elementary mode analysis with regulation

Molecular Networks B SS13

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25.04.13

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Jungreuthmayer and Zanghellini *BMC Systems Biology* 2012, **6**:103
http://www.biomedcentral.com/1752-0509/6/103

BMC Systems Biology

METHODOLOGY ARTICLE Open Access

Designing optimal cell factories: integer programming couples elementary mode analysis with regulation

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Overview

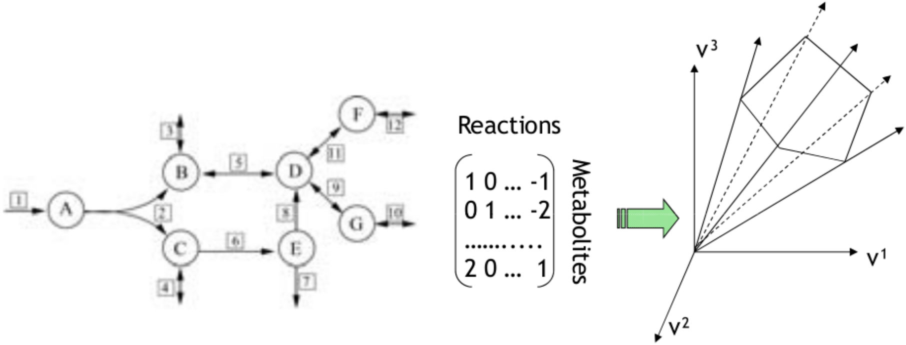
Background and Motivation

- microbes can be used for metabolic engineering e.g. ethanol production in *E. coli*
- Methabolic networks are available for some model organisms

Gaol

Gene deletion strategie to optimize the production efficiency of strains.

Metabolic network



source A.Bockmayer lecture slides Algorithms in Systembiology SS12
Model of metabolic network with

- m internal metabolites
- n reactions
- $S \in \mathbb{R}^{m \times n}$ stoichiometric matrix
- $\hat{v} \in \mathbb{R}^{n}$ flux vector

fig?

Steady state assumption

Steady state assumption

Metabolite concentrations and reaction rates are constant.

$$S \cdot \hat{v} = 0 \tag{1}$$

Steady state flux coen:
$C = \{v \in \mathbb{R}^n | Sv = 0, v_i \geq 0, i \in Irr\}$

Elementary mode analysis

- For $v \in \mathbb{R}^n$, the support of v is defined as $supp(v) = \{i \in \{1, ..., n\} | v_i \neq 0\}$
- $v \in C$ is an *elementary flux mode* if $supp(v)$ is minimla w.r.t $\subseteq$ i.e, if there is no $v' \in C, v' \neq 0$ with $supp(v') \subsetneq supp(v)$.

Definition

An elementary mode (EM) is a minimal and indivisible set of reactions that operates under steady state conditions, while obeying all (ir-)reersibility constraints.

Network of minimal functionality (NMF)

Theory: Elementary mode analysis

$e = e(\hat{e})$ is the binary representation of a EM e.

$$e_i := e(\hat{e}_i)) = \begin{cases} 1 & \text{if } \hat{e}_i \neq 0 \\ 0 & \text{if } \hat{e}_i = 0 \end{cases} \quad (2)$$

$e^T v \leq e^T e = \sum_{i=1}^{n} e_i^2 = \sum_{i=1}^{n} e_i =: ||e||$

Binary integer program

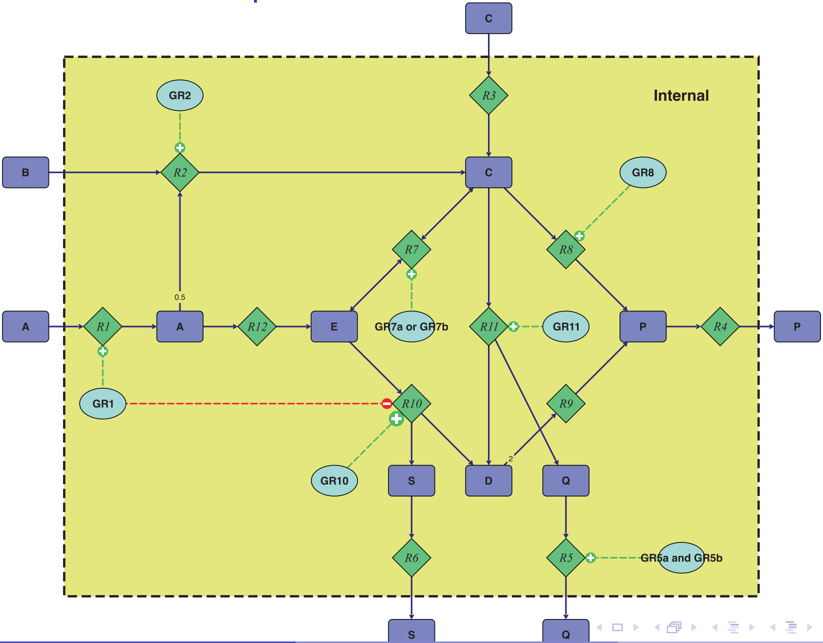
Group all q elementary modes:

$$
\begin{aligned}
G &:= (e_1, ..., e_r)^T && \textit{goal matrix} \text{ with desirable EM} \\
H &:= (e_{r+1}, ..., e_{r+s})^T && \textit{helper matrix} \text{ tolerated EM} \\
K &:= (e_{r+s+1}, ..., e_{r+s+t})^T && \textit{kill matrix} \text{ unwanted EM}
\end{aligned}
$$

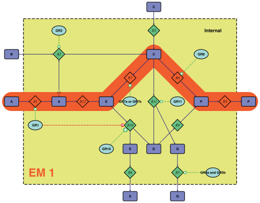
$max||x||$
s.t.

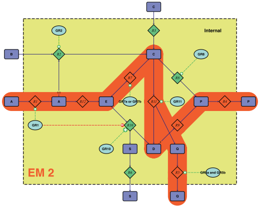
$$
\begin{aligned}
e_g^T x &= ||e_g|| && g \in \{1, ..., r\} \\
e_h^T x &\leq ||e_h|| && h \in \{r+1, ..., r+s\} \\
e_k^T x &\leq ||e_k|| - 1 && k \in \{r+s+1, ..., r+s+t\}
\end{aligned}
$$

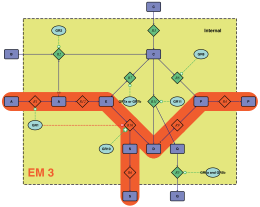
Illustrative example

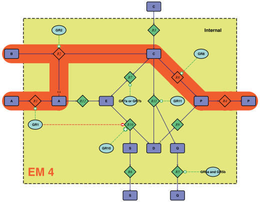


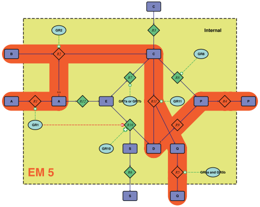
Elementary Modes

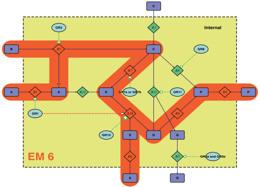


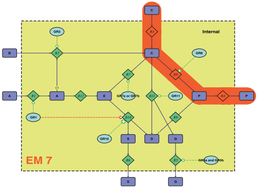


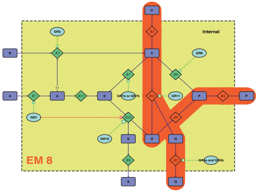


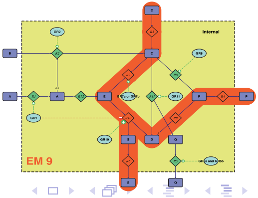












Introduction: Fixed Point Analysis

Given the system of differential equations:

$$y' = f(y)$$

Definition

A *fixed point* y^* is defined by $f(y^*) = 0$.

- Solve the equation $f(y) = 0$
- Analyse eigenvalues of the Jacobian at fixed points.

Now: System with *controle parameter* μ.

$$y' = f(y, \mu)$$

How does μ influence the number, location and stability of fixed points?

Elementary flux mode

For $v \in R$