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

Molecular Networks B SS13

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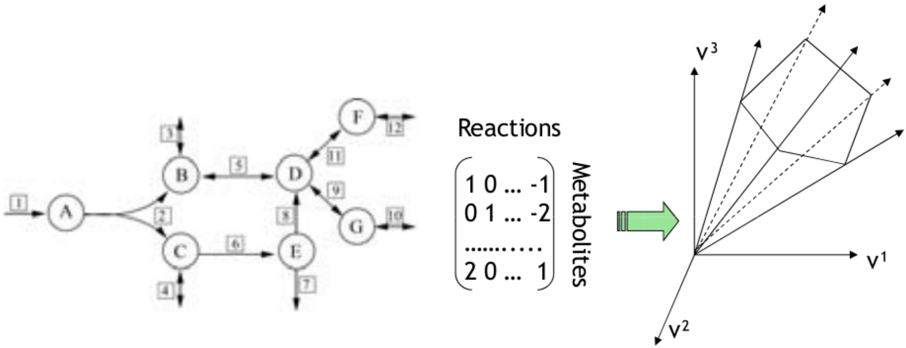
Overview

1. Introduction and Repetition
2. Motivation and Theory
3. Illustrative example
4. Including regulation
5. (Optimizing metabolic functionality)
6. Realistic example: Ethanol production in E. coli
7. Summary and conclusions

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

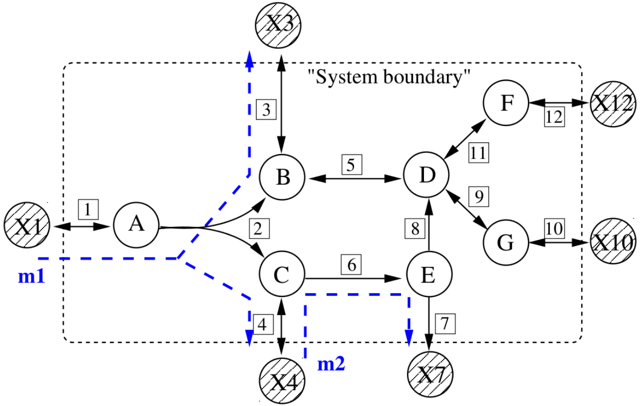
Elementary mode analysis

- 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

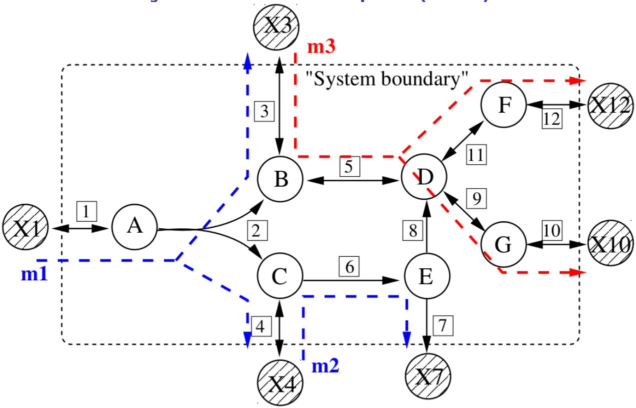
An elementary mode (EM) is a minimal and indivisible set of reactions that operates under steady state conditions, while obeying all (ir-)reversibility constraints.

Elementary mode example



- $m^1 = (1, 1, 1, 1, 0, 0, 0, 0, 0, 0, 0, 0)$
- $m^1 = (0, 0, 0, -1, 0, 1, 1, 0, 0, 0, 0, 0)$
- m^1 and m^2 are elementary modes.

Elementary mode example (ctd)



- $m^3 = (0, 0, 2, 0, 2, 0, 0, 0, 1, 1, 1, 1)$
- $m^3 = m^4 + m^5$, with
  - $m^4 = (0, 0, 1, 0, 1, 0, 0, 0, 1, 1, 0, 0)$
  - $m^5 = (0, 0, 1, 0, 1, 0, 0, 0, 0, 0, 1, 1)$
- Since $m^4, m^5 \in C, supp(m^4), supp(m^5) \subsetneq supp(m^3)$, m^3 is not an elementary flux mode.

Paper and authors

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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.

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:

$$G := (e_1, ..., e_r)^T \qquad \textit{goal matrix} \text{ with desirable EM}$$

$$H := (e_{r+1}, ..., e_{r+s})^T \qquad \textit{helper matrix} \text{ tolerated EM}$$

$$K := (e_{r+s+1}, ..., e_{r+s+t})^T \qquad \textit{kill matrix} \text{ unwanted EM}$$

$max||x||$

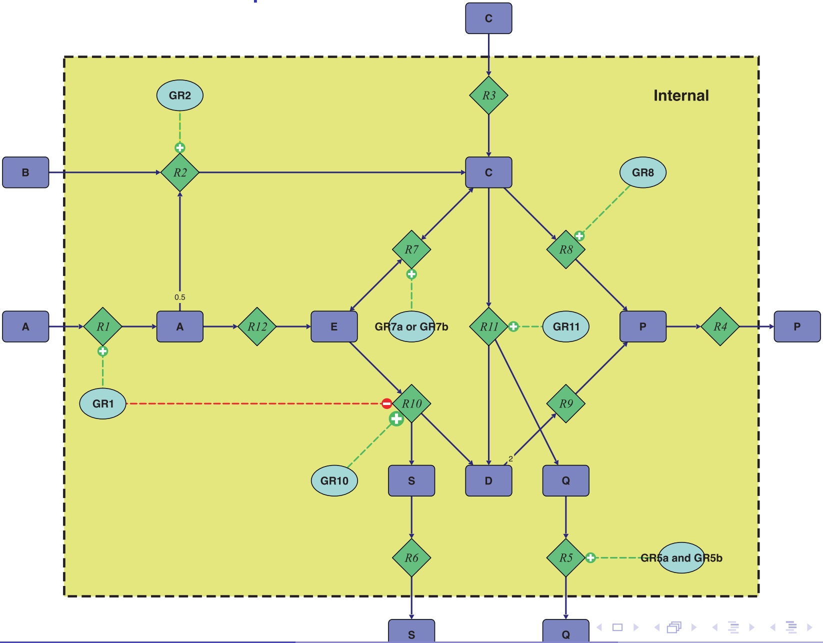
s.t.

$$e_g^T x = ||e_g|| \qquad g \in \{1, ..., r\}$$

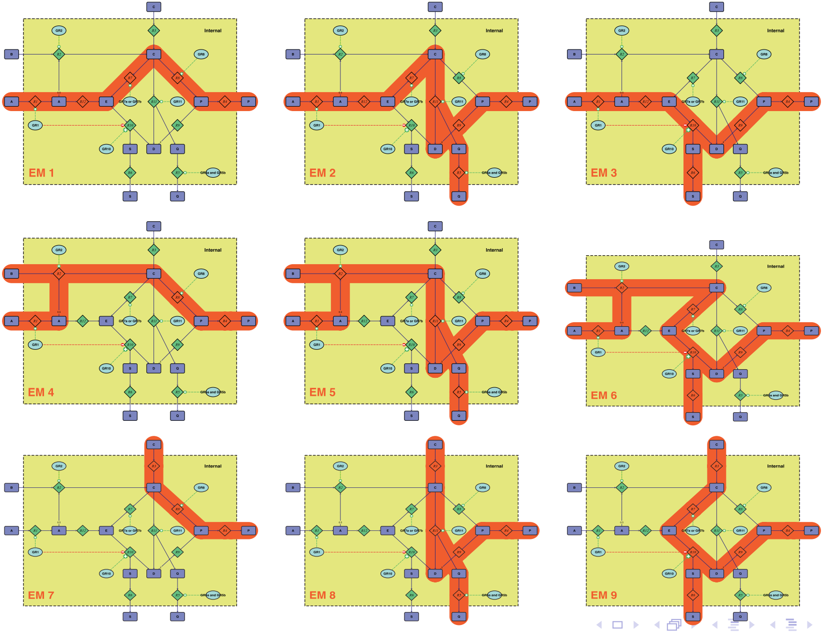
$$e_h^T x \leq ||e_h|| \qquad h \in \{r+1, ..., r+s\}$$

$$e_k^T x \leq ||e_k|| - 1 \qquad k \in \{r+s+1, ..., r+s+t\}$$

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 $v \in R$