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

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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 and steady state assumption

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

Assume metabolite concentrations and reaction rates are constant.

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

Elementary mode analysis

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.

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

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

Binary integer program

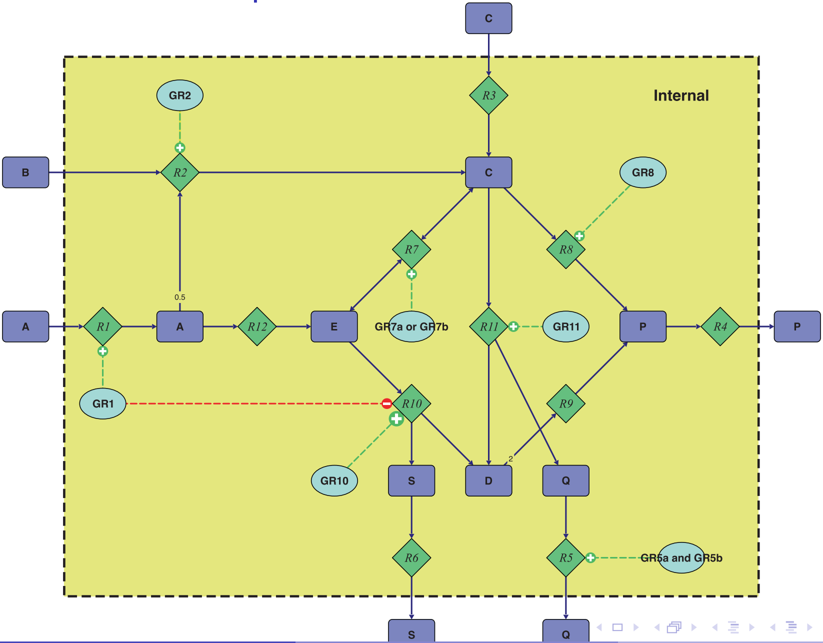
Group all q elementary modes:

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

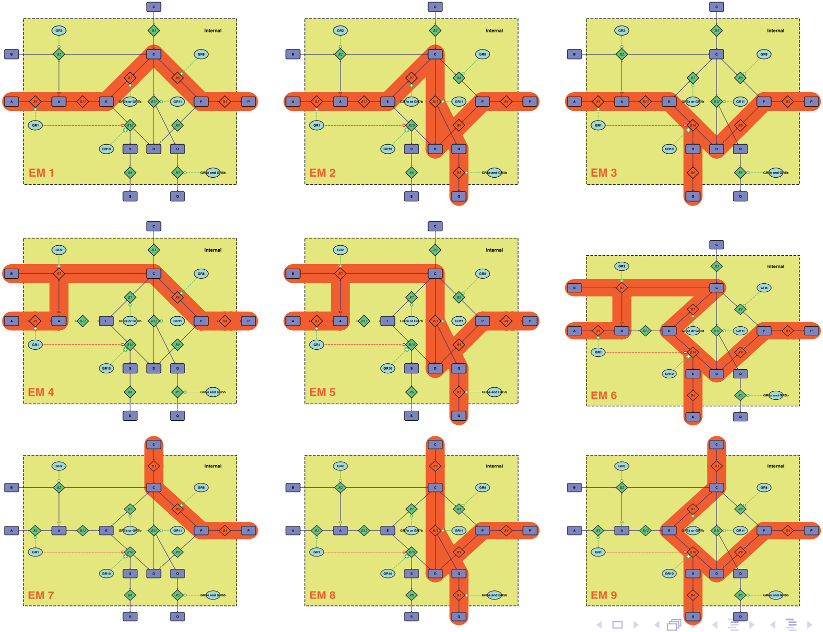
$max||x||$
s.t.

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

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 $v \in R$