9. Minimal metabolic behaviors (MMBs)

Larhlimi/Bockmayr 09

- Consider outer descriptions of the flux cone C.
- Characterize C directly by its minimal proper faces and the lineality space.
- The lineality space $\mathrm{linsp}(C) = \{v \in C \mid v_i = 0, \text{ for all } i \in Irr\}$ has a natural description by equality constraints
  $\rightsquigarrow$ reversible metabolic space.
- Each minimal proper face can be characterized by a unique set of inequality constraints (= irreversible reactions)
  $\rightsquigarrow$ minimal metabolic behaviors (MMBs).
- The resulting outer description is both minimal and unique.

Metabolic behaviors

- A metabolic behavior is a set of irreversible reactions $D \subseteq Irr, D \neq \emptyset$, such that there exists a flux vector $v \in C$ with

$$D = \{i \in Irr \mid v_i \neq 0\}.$$

- A metabolic behavior D is minimal, if there is no metabolic behavior $D' \subsetneq D$ strictly contained in D.

Elementary modes vs. MMBs

- If $v \in C$ is an elementary flux mode, then the set

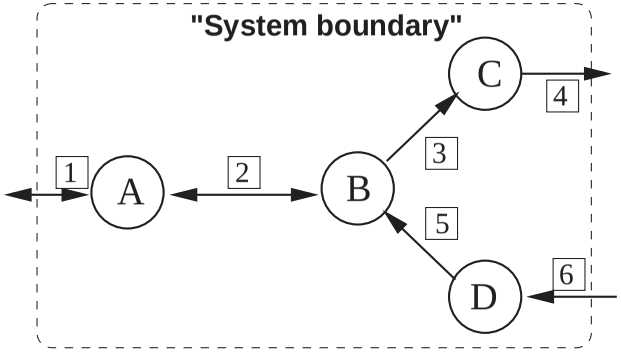
$$supp(v) = \{i \in \{1, \ldots, n\} \mid v_i \neq 0\}$$

  is a minimal set of active reactions.
- Similarly, a minimal metabolic behavior

$$\{i \in Irr \mid v_i > 0\} = \{i \in Irr \mid v_i \neq 0\},$$

  for some $v \in C$, is a minimal set of active irreversible reactions.

Example



$e^1 = (1,1,1,1,0,0)$, $e^2 = (-1,-1,0,0,1,1)$, $e^3 = (0,0,1,1,1,1)$
$D^1 = \{3,4\}$ $D^2 = \{5,6\}$

Characteristic set of a minimal face

- Lemma Given a minimal proper face G of C and an irreversible reaction $j \in Irr$, the following are equivalent:
  - $v_j > 0$, for some $v \in G \setminus \mathrm{linsp}(C)$.
  - $v_j > 0$, for all $v \in G \setminus \mathrm{linsp}(C)$.
- Call

$$D = D_G = \{j \in Irr \mid v_j > 0, \text{ for all } v \in G \setminus \mathrm{linsp}(C)\}$$

  the characteristic set of G.
- It follows

$$G = \{v \in C \mid v_j > 0, j \in D, \ \ v_i = 0, i \in Irr \setminus D\} \ \cup \ \mathrm{linsp}(C).$$

MMBs and minimal faces

Theorem

Let $C = \{v \in \mathbb{R}^n \mid Sv = 0, \ v_i \geq 0, i \in Irr\}$ be the flux cone of a metabolic network.
For any set of irreversible reactions $D \subseteq Irr$, the following are equivalent:

- D is a minimal metabolic behavior.
- There exists a minimal proper face G of C whose characteristic set is D.

MIP to enumerate shortest MMBs/GFMs

Rezola et al. 11

$$\min W \cdot \textstyle\sum_{j \in Irr} z_j + \sum_{j \notin Irr} z_j$$

$$\begin{aligned} & Sv = 0, v_{Irr} \geq 0, \\ & -Mz_j \leq v_j \leq Mz_j, \quad \text{for } j = 1, \ldots, n, \\ & \textstyle\sum_{j \in Irr} v_j \geq 1, \\ & v \in \mathbb{R}^n, z \in \{0,1\}^n \end{aligned}$$

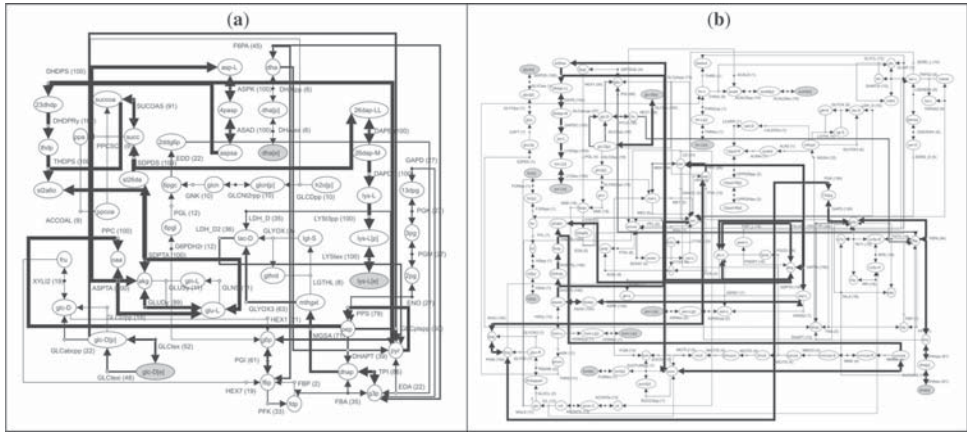
Forbidding the k-th solution (v^k, z^k): Let $D^k = \{j \in Irr \mid z_j^k = 1\}$.

$$\sum_{j \in D^k} z_j \leq |D^k| - 1, \text{ for } k = 1, \ldots, K-1.$$

v^k is called the k-th generating flux mode (GFM)

EFMs vs. GFMs in *E. coli*

Rezola et al. 11



(thickness of arrows proportional to the number of times a reaction appears in the 100 shortest EFMs / GFMs)

EFMs vs. GFMs in *E. coli* (2)

	NoR	LI	OvR	AHD	No EFMs	No EFMs(R)
100 shortest EFMs	54	25–26	90.74% (49/54)	12.79	1665 Lys: 1636	5398 Lys: 3960
100 shortest GFMs	132	25–37	37.12% (49/132)	16.21	354238 Lys: 25007	$5 \times 10^5 - 5 \times 10^{10}$ Lys: $*$

NoR, number of reactions; LI, length interval; OvR, overlapping percentage of reactions of the 100 shortest EFMs (GFMs) in the shortest GFMs (EFMs); AHD, average hamming distance; No EFMs, number of EFMs emerging from the network formed by the 100 shortest EFMs (GFMs); No EFMs (R), number of EFMs emerging from the network formed by the 100 shortest EFMs (GFMs) and the reversible metabolic space (RMS); Lys, L-lysine.

Novel pathway for lysine production