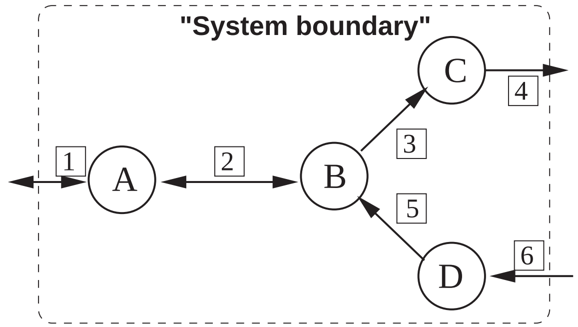
6. Elementary flux modes

Schuster/Hilgetag'94

- $C = \{v \in \mathbb{R}^n \mid Sv = 0,\ v_i \geq 0, i \in Irr\}$ steady-state flux cone
- Support of $v \in \mathbb{R}^n$: $supp(v) = \{i \in \{1,\ldots,n\} \mid v_i \neq 0\}$.
- Elementary flux mode (EFM):
  Flux vector $v \in C$ with minimal support, i.e., there is no $v' \in C, v' \neq 0$ with $supp(v') \subsetneqq supp(v)$.

Example



$$e^1 = (1,1,1,1,0,0),\quad e^2 = (-1,-1,0,0,1,1),\quad e^3 = (0,0,1,1,1,1)$$

Basic properties (1)

Proposition Let $e \in C$ be an EFM. If $v \in C$ with $supp(v) = supp(e)$. Then $v = \lambda e$, for some $\lambda \in \mathbb{R} \setminus \{0\}$.

$\rightsquigarrow$ EFMs are uniquely determined by their support.

Proof: Let $D = supp(v)$.
Let S_D be the submatrix of S with columns corresponding to D.
Then $rg(S_D) < |D|$ and $rg(S_{D\setminus\{j\}}) = |D| - 1$, for any $j \in D$.
This implies $rg(S_D) = |D| - 1$, i.e., the set of solutions of the linear equation system $S_D v_D = 0$ is a one-dimensional linear subspace.

Basic properties (2)

Proposition A flux vector $v \in C$ is an EFM iff there exist no $v^1, v^2 \in C \setminus \{0\}$ s.t. $supp(v^1), supp(v^2) \subsetneqq supp(v)$, $v = v^1 + v^2$.

$\rightsquigarrow$ EFMs correspond to irreducible elements of the flux cone.

Proof: "$\Rightarrow$:" Suppose $v \in C$ is an EFM and reducible.
Choosing $v' = v^1$ gives directly a contradiction.

"$\Leftarrow$:" Suppose $v \in C$ is irreducible and not an EFM.
Then there exists $v' \in C \setminus \{0\}$ with $supp(v') \subsetneqq supp(v)$.
If $supp(v) \cap Irr = \emptyset$, choose some $k \in supp(v)$ arbitrary and let $\lambda = v_k / v'_k$.
Otherwise, let $\lambda = \min\{v_i / v'_i \mid i \in supp(v) \cap Irr\}$ and choose $k \in supp(v) \cap Irr$ such that $\lambda = v_k / v'_k$.
Define $v^1 = \lambda v'$ and $v^2 = v - v^1$.

Basic properties (3)

Proposition Any $v \in C$ can be written as a non-negative linear combination of EFMs:

$$v = \sum_{e \in EFM} \lambda_e e, \quad \lambda_e \geq 0$$

$\rightsquigarrow$ EFMs define a finite conic basis of the flux cone.

Proof: If $v \in C \setminus \{0\}$ is not an EFM, it can be decomposed into $v = v^1 + v^2$, with $supp(v^1), supp(v^2) \subsetneq supp(v)$.
Since all supports are finite sets, this can be repeated only finitely many times.

Note: In general, the decomposition is not unique.

Computing EFMs

- If all reactions are irreversible, EFMs correspond to extreme rays of the flux cone (Gagneur/Klamt 04).
- EFMs can be computed by algorithms that enumerate the extreme rays of a pointed cone $\rightsquigarrow$ double description method
- Software
  - Metatool (Pfeiffer et al. 99, Univ. Jena)
  - efmtool (Terzer 09, ETH Zurich)
- Enumerating EFMs is computionally hard (Acuña et al. 09 and 10).

MILP to enumerate shortest EFMs

de Figueiredo et al. 09

Assume all reactions are irreversible.

$$\min \sum_{j=1}^{n} a_j$$

$$\begin{aligned} & Sv = 0, v \geq 0, \\ & a_j \leq v_j \leq M a_j, \quad \text{for } j = 1, \ldots, n, \quad \text{“BigM”} \\ & \textstyle\sum_{j=1}^{n} a_j \geq 1, \\ & v \in \mathbb{R}^n, a \in \{0,1\}^n \end{aligned}$$

Forbidding the i-th solution (v^i, a^i):

$$\sum_{j \in supp(v^i)} a_j \leq |supp(v^i)| - 1, \quad \text{for } i = 1, 2, \ldots, k \quad \text{“no-good cut”}$$

Flux coupling relations (reminder)

Burgard et al. 04

- $C = \{v \mid Sv = 0, \ v_k \geq 0, k \in Irr\}$ flux cone
- A reaction i is blocked if $v_i = 0$, for all $v \in C$.
- Let i and j be two unblocked reactions.
  - i is directionally coupled to j, $i \overset{=0}{\rightarrow} j$, if for all $v \in C$, $v_i = 0$ implies $v_j = 0$.
  - i and j are partially coupled, $i \overset{=0}{\leftrightarrow} j$, if for all $v \in C$, $v_i = 0$ is equivalent to $v_j = 0$.
  - i and j are fully coupled, $i \frown^{\lambda} j$, if there exists $\lambda \in \mathbb{R} \setminus \{0\}$ such that for all $v \in C, v_j = \lambda v_i$.

Flux coupling and EFMs

Marashi/Bockmayr 11

Proposition

Let $\mathscr{N}$ be a metabolic network with flux cone C and set of elementary modes E.

For any two reactions i and j, the following are equivalent:

(i) For all $v \in C$, $v_i = 0$ implies $v_j = 0$.

(ii) For all $e \in E$, $e_i = 0$ implies $e_j = 0$.

Flux coupling and EFMs (ctd)

Corollary

Let i, j be two non-blocked reactions in a metabolic network $\mathscr{N}$ with set of elementary modes E. Then:

- $i \stackrel{=0}{\rightarrow} j$ iff for all $e \in E$, $e_i = 0$ implies $e_j = 0$.
- $i \stackrel{=0}{\leftrightarrow} j$ iff for all $e \in E$, $e_i = 0$ is equivalent to $e_j = 0$.
- $i \backsim^{\lambda} j$ iff there exists $\lambda \neq 0$ such that for all $e \in E$, $e_j = \lambda \cdot e_i$.

Flux uncoupling

- Two reactions i, j are uncoupled if neither $i \stackrel{=0}{\rightarrow} j$ nor $j \stackrel{=0}{\rightarrow} i$.
- Equivalently, there exist EFMs $e, e' \in E$ such that

$$e_i = 0,\ e_j \neq 0 \quad \text{and} \quad e'_i \neq 0,\ e'_j = 0.$$

- Two uncoupled reactions i, j are called mutually exclusive if there is no EFM $e \in E$ with

$$e_i \neq 0,\ \ e_j \neq 0.$$

(i and j never occur together in the same EFM).