



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 $v \in \mathbb{R}^n$: $supp(v) = \{i \in \{1, \dots, n\} \mid v_i \neq 0\}$.
- ▷ **Elementary flux mode (EFM)**: Flux vector $v \in C \setminus \{0\}$ with **minimal support**, i.e., there is no $v' \in C \setminus \{0\}$ with $supp(v') \subsetneq supp(v)$.



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

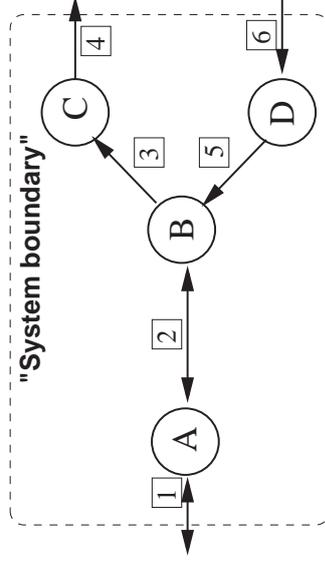
↪ EFMs are uniquely determined by their support.

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.



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



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

↪ 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 $supp(v') \subsetneq supp(v)$.

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 $v^2 = v - v^1$.



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

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

\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 $\text{supp}(v^1), \text{supp}(v^2) \subsetneq \text{supp}(v)$. Since all supports are finite sets, this can be repeated only finitely many times.

Note: In general, the decomposition is not unique.



- ▷ 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 computationally hard (Acuña et al. 09 and 10).



MILP to enumerate shortest EFMs

de Figueiredo et al. 09

Assume all reactions are irreversible.

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

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

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