6. Elementary flux modes

Schuster/Hilgetag’94

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

Basic properties (1)

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

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

Example

```
A    B
|    |
1    2

C    D
|    |
3    5
```

“System boundary”

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

Basic properties (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. \( \text{supp}(v^1), \text{supp}(v^2) \subsetneq \text{supp}(v) \), \( v = v^1 + v^2 \).

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 \( \text{supp}(v') \subsetneq \text{supp}(v) \).
If \( \text{supp}(v) \cap \text{Irr} = \emptyset \), choose some \( k \in \text{supp}(v) \) arbitrary and let \( \lambda = v_k / v'_k \).
Otherwise, let \( \lambda = \min \{ v_i / v'_i \mid i \in \text{supp}(v) \cap \text{Irr} \} \) and choose \( k \in \text{supp}(v) \cap \text{Irr} \) 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:

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

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.

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 **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.

\[
\begin{align*}
\text{min} & \quad \sum_{j=1}^{n} a_j \\
Sv &= 0, \quad v \geq 0, \\
a_j &\leq v_j \leq Ma_j, \quad \text{for } j = 1, \ldots, n, \quad \text{“BigM”} \\
\sum_{j=1}^{n} a_j &\geq 1, \\
v &\in \mathbb{R}^n, \quad a \in \{0, 1\}^n
\end{align*}
\]

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

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