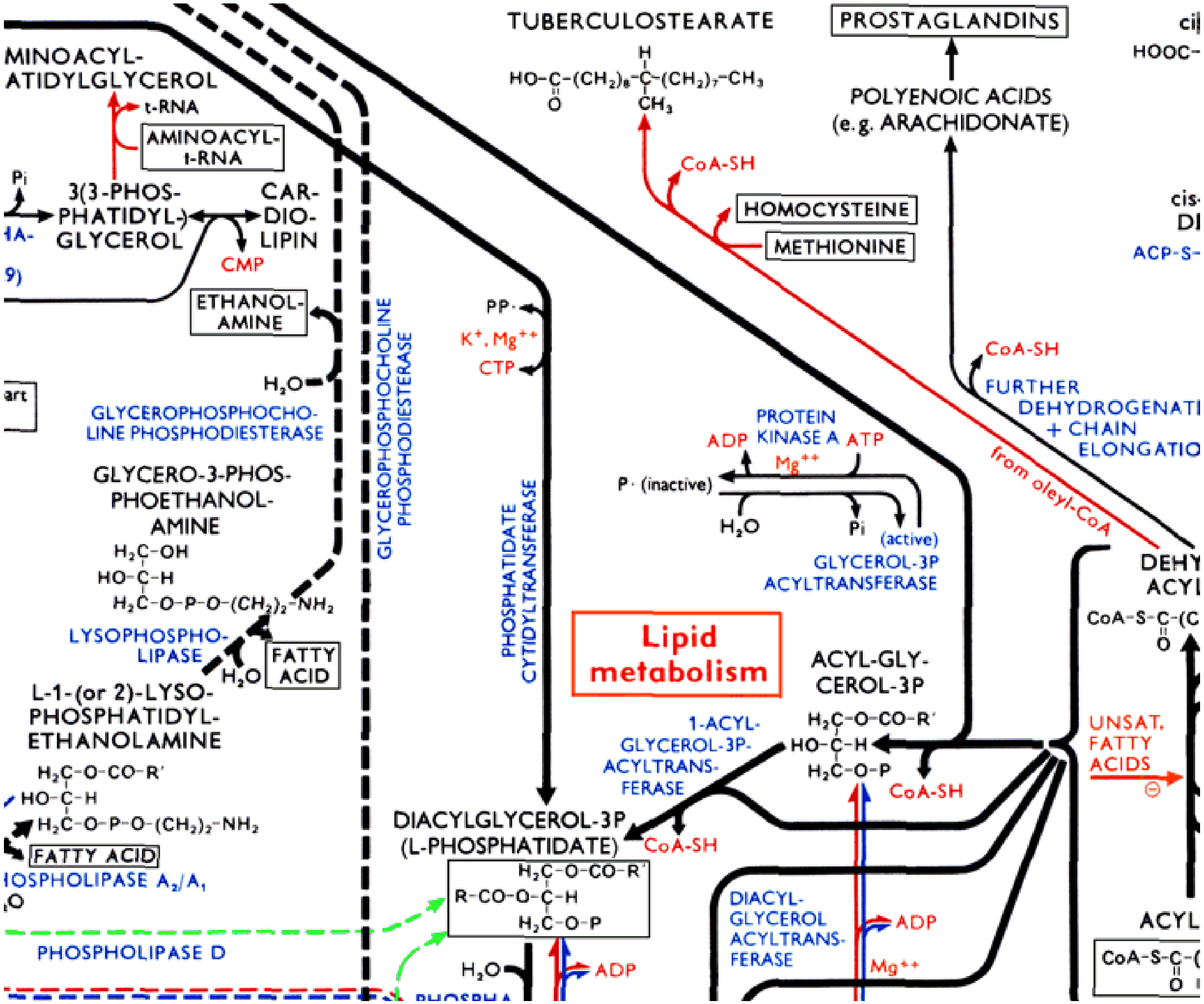
Metabolic network



Questions

- Network consistency $\rightsquigarrow$ blocked reactions, missing network elements
- Functional pathways and cycles $\rightsquigarrow$ possible routes between specific inputs and outputs
- Network capabilities $\rightsquigarrow$ maximal product yield
- Importance of reactions, correlated reactions $\rightsquigarrow$ flux coupling
- Network design $\rightsquigarrow$ effect of adding/deleting reactions, minimum cut sets
- Network flexibility and robustness $\rightsquigarrow$ tolerance w.r.t. changes, set of all possible behaviors

Steady state assumption

- Dynamic modeling $\rightsquigarrow$ changes in species concentration

$$\frac{dc(t)}{dt} = S \cdot v(t)$$

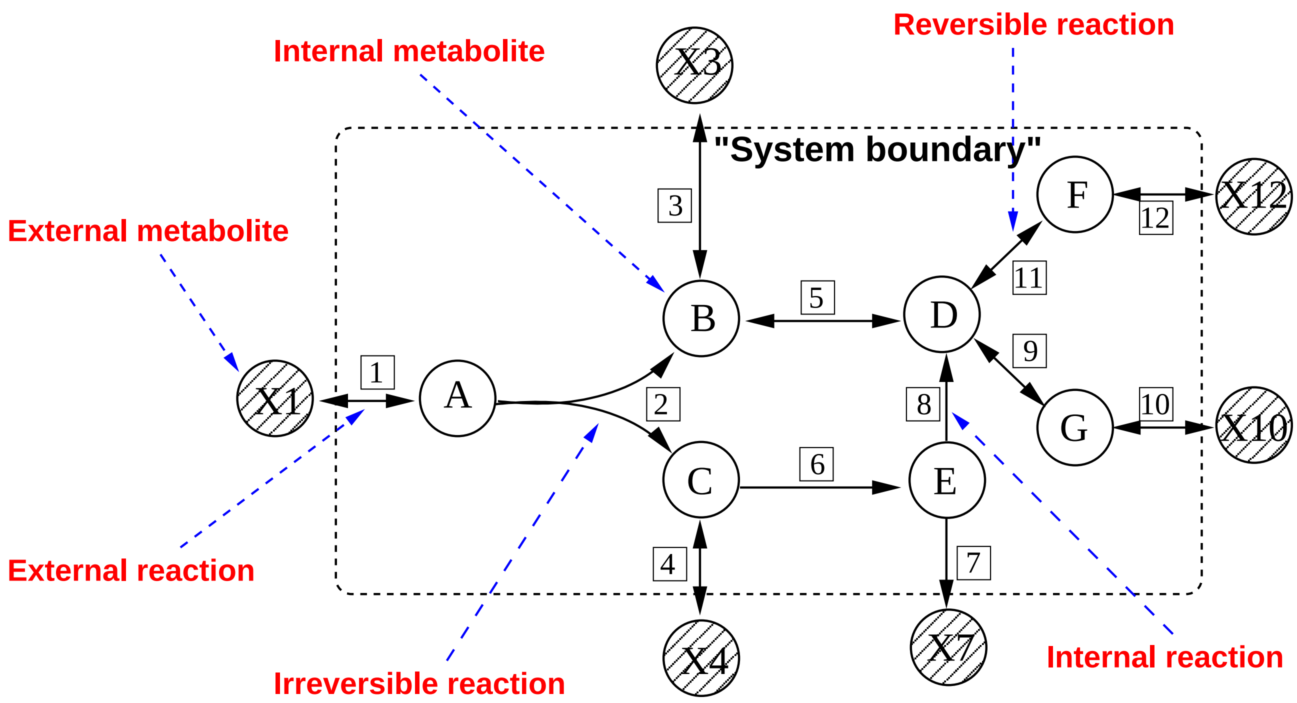
- S stoichiometric matrix (S_{ij}: stoichiometric coefficient of reactant i in reaction j)

- $v(t)$ flux distribution or reaction rates, approximately $v(t) = f(c(t), p, t)$, with parameter vector p.

- Steady state assumption: Assume metabolic concentrations and reaction rates are constant (on longer time scales).

- Metabolic balancing equation: $Sv = 0$

Metabolic network



Stoichiometry and Irreversibility

- Stoichiometric matrix $S \in \mathbb{R}^{m \times n}$
  - Rows $\rightsquigarrow$ internal metabolites $i = 1, \ldots, m$
  - Columns $\rightsquigarrow$ internal and external reactions $j = 1, \ldots, n$
- v_j: flux through reaction j at steady state $v \in \mathbb{R}^n$
- Stoichiometric constraints/flux balance principle: $Sv = 0$
- Thermodynamic constraints: $v_i \geq 0, i \in Irr$
- Steady-state flux cone

$$C = \{v \in \mathbb{R}^n \mid Sv = 0,\ v_i \geq 0, i \in Irr\}$$

$\rightsquigarrow$ describes all possible flux distributions

Polyhedral cones

- Convex cone: $C \subseteq \mathbb{R}^n$, with $\lambda x + \mu y \in C$ whenever $x, y \in C$ and $\lambda, \mu \geq 0$.

- Polyhedral cone: $C = \{x \in \mathbb{R}^n \mid Ax \geq 0\}$, for some $A \in \mathbb{R}^{m \times n}$.

- Finitely generated cone

$$C = \text{cone}\{g^1, \ldots, g^s\} = \{\lambda_1 g^1 + \cdots + \lambda_s g^s \mid \lambda_1, \ldots, \lambda_s \geq 0\},$$

for some $g^1, \ldots, g^s \in \mathbb{R}^n$.

- Theorem (Farkas-Minkowski-Weyl)
A convex cone is polyhedral if and only if it is finitely generated.

Describing the flux cone

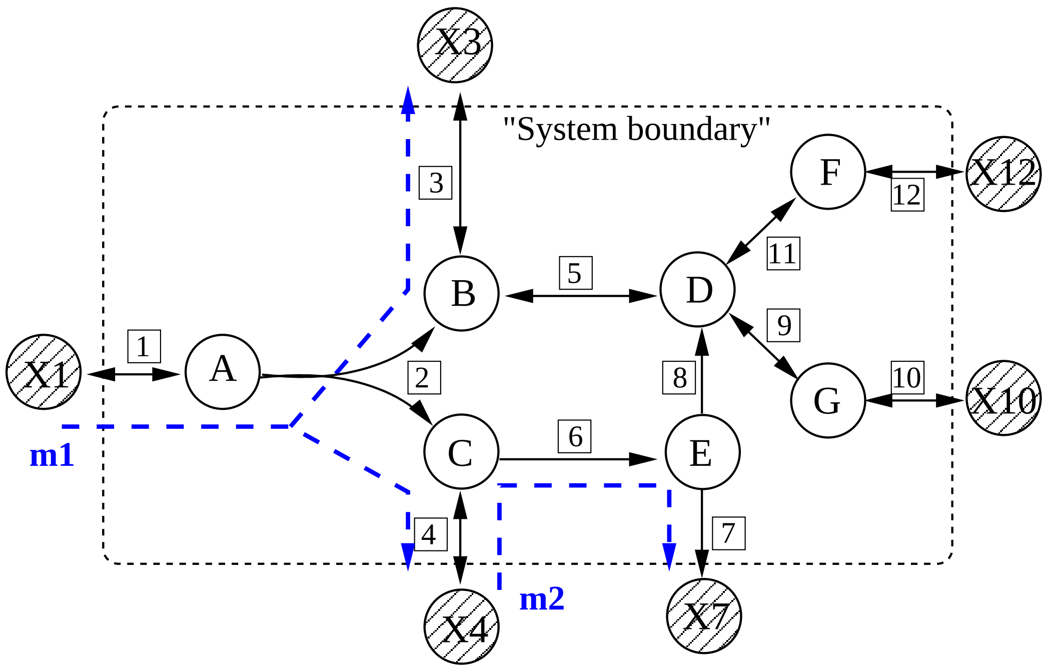
- Inner descriptions $\rightsquigarrow$ flux vectors
  - Elementary flux modes (Schuster et al.):
    unique for pointed and non-pointed cones, not minimal.
  - Extreme pathways (Palsson et al.):
    minimal and unique for pointed cones $\rightsquigarrow$ reconfiguration of the network
    not minimal for non-pointed cones.
- Outer descriptions $\rightsquigarrow$ linear inequalities/irreversible reactions
  - Minimal metabolic behaviors and the reversible metabolic space (Larhlimi/Bockmayr):
    minimal and unique for general cones.

Elementary flux modes

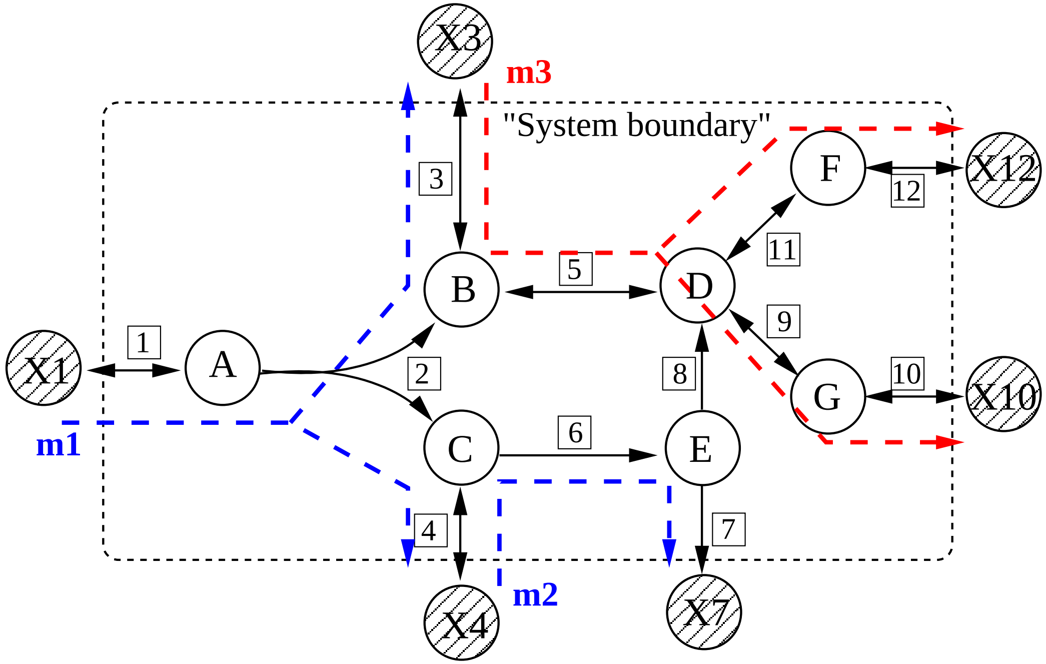
Schuster et al.

- $C = \{v \in \mathbb{R}^n \mid Sv = 0,\ v_i \geq 0, i \in Irr\}$ steady-state flux cone
- For $v \in \mathbb{R}^n$, let $Z(v) = \{i \in \{1, \ldots, n\} \mid v_i = 0\}$.
- $v \in C$ is an elementary flux mode if there do not exist $v', v'' \in C$, with $Z(v) \subsetneq Z(v')$, $Z(v) \subsetneq Z(v'')$ such that $v = v' + v''$.
- Equivalently, $v \in C$ is an elementary flux mode if there is no $v' \in C, v' \neq 0$ with $Z(v) \subsetneq Z(v')$.
- Finite set of generating vectors with maximum number of zero components, however not minimal.

Example



- $m^1 = (1, 1, 1, \ \ 1, 0, 0, 0, 0, 0, 0, 0, 0)$
- $m^2 = (0, 0, 0, -1, 0, 1, 1, 0, 0, 0, 0, 0)$
- m^1 and m^2 are elementary modes.



- $m^3 = (0, 0, 2, 0, 2, 0, 0, 0, 1, 1, 1, 1)$

- $m^3 = m' + m''$, with
  - $m' = (0, 0, 1, 0, 1, 0, 0, 0, 1, 1, 0, 0)$,
  - $m'' = (0, 0, 1, 0, 1, 0, 0, 0, 0, 0, 1, 1)$

- Since $m', m'' \in C, Z(m^3) \subsetneq Z(m'), Z(m^3) \subsetneq Z(m'')$, m^3 is not an elementary flux mode.