- If $u \not\geq 0$, choose $i \in I$ such that $u_i < 0$ and define the direction $d \stackrel{\text{def}}{=} -A_{I*}^{-1} e_i$, where $e_i$ is the $i$-th unit basis vector in $\mathbb{R}^I$.
- Next increase the objective function value by going from $v$ in direction $d$, while maintaining feasibility.

## Simplex Algorithm: Algebraic version (2)

1. If $Ad \not\leq 0$, the largest $\lambda \geq 0$ for which $v + \lambda d$ is still feasible is

$$\lambda^* = \min\{\frac{b_p - A_{p*} v}{A_{p*} d} \mid p \in \{1, \ldots, m\}, A_{p*} d > 0\}. \tag{PIV}$$

   Let this minimum be attained at index $k$. Then $k \notin I$ because $A_{I*} d = -e_i \leq 0$.

   Define $I' = (I \setminus \{i\}) \cup \{k\}$, which corresponds to the vertex $v + \lambda^* d$.

   Replace $I$ by $I'$ and repeat the iteration.

2. If $Ad \leq 0$, then $v + \lambda d$ is feasible, for all $\lambda \geq 0$. Moreover,

$$c^T d = -c^T A_{I*}^{-1} e_i = -u^T e_i = -u_i > 0.$$

   Thus the objective function can be increased along $d$ to infinity and the problem is unbounded.

## Termination and complexity

- The method terminates if the indices $i$ and $k$ are chosen in the right way (such choices are called *pivoting rules*).
- Following the rule of Bland, one can choose the smallest $i$ such that $u_i < 0$ and the smallest $k$ attaining the minimum in (PIV).
- For most known pivoting rules, sequences of examples have been constructed such that the number of iterations is exponential in $m + n$ (e.g. Klee-Minty cubes).
- Although no pivoting rule is known to yield a polynomial time algorithm, the Simplex method turns out to work very well in practice.

## Simplex : Phase I

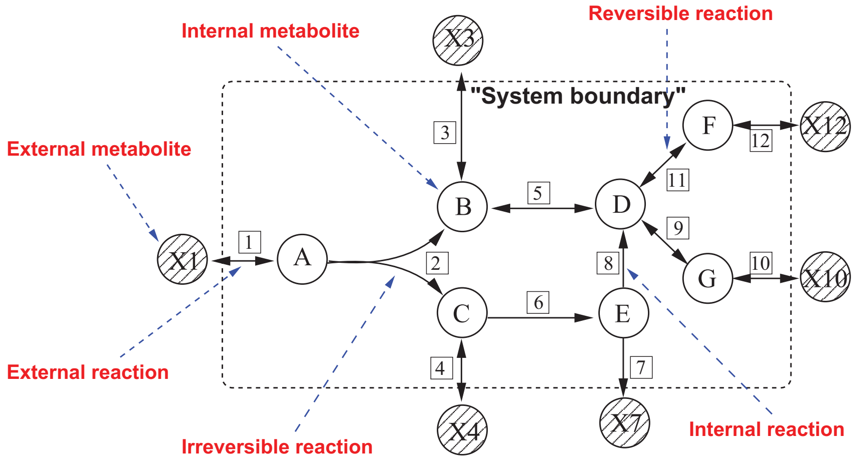
- In order to find an *initial feasible basis*, consider the auxiliary linear program

$$\max\{y \mid Ax - by \leq 0, \ \ -y \leq 0, \ \ y \leq 1\}, \tag{Aux}$$

   where $y$ is a new variable.

- Given an arbitrary basis $K$ of $A$, obtain a feasible basis $I$ for (Aux) by choosing $I = K \cup \{m+1\}$. The corresponding basic feasible solution is 0.
- Apply the Simplex method to (Aux). If the optimum value is 0, then (LP) is infeasible. Otherwise, the optimum value has to be 1.
- If $I'$ is the final feasible basis of (Aux), then $K' = I' \setminus \{m+2\}$ can be used as an initial feasible basis for (LP).

## Application: Metabolic networks



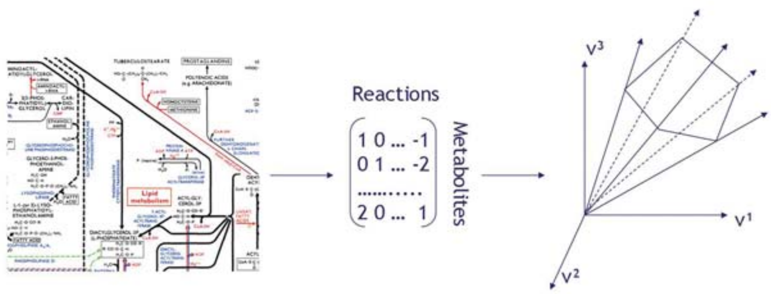

## Stoichiometric matrix

- Metabolites (internal) $\rightsquigarrow$ rows
- Biochemical reactions $\rightsquigarrow$ columns

$$\text{Reaction}\quad kA + lC \xrightarrow{j} mE + nH \qquad \text{gives} \qquad \begin{array}{c} A \\ B \\ C \\ D \\ E \\ F \\ G \\ H \end{array} \begin{pmatrix} \dots & -k & \dots \\ & 0 & \\ & -l & \\ & 0 & \\ & m & \\ & 0 & \\ & 0 & \\ \dots & n & \dots \end{pmatrix}$$

## Flux cone

- Flux balance: $Sv = 0$
- Irreversibiliy of some reactions: $v_i \geq 0, i \in Irr$.
- *Steady-state flux cone* $C = \{v \in \mathbb{R}^n \mid Sv = 0, v_i \geq 0, \text{ for } i \in Irr\}$




## Flux balance analysis

- Use linear programming to study flux distribution in a cell

$$\max\{c^T v \mid Sv = 0, \;\; v_{\min} \leq v \leq v_{\max}\}$$

- Objective function
  - Maximize biomass production
  - Maximize metabolite production (e.g. biofuel)
- *Metabolic engineering*