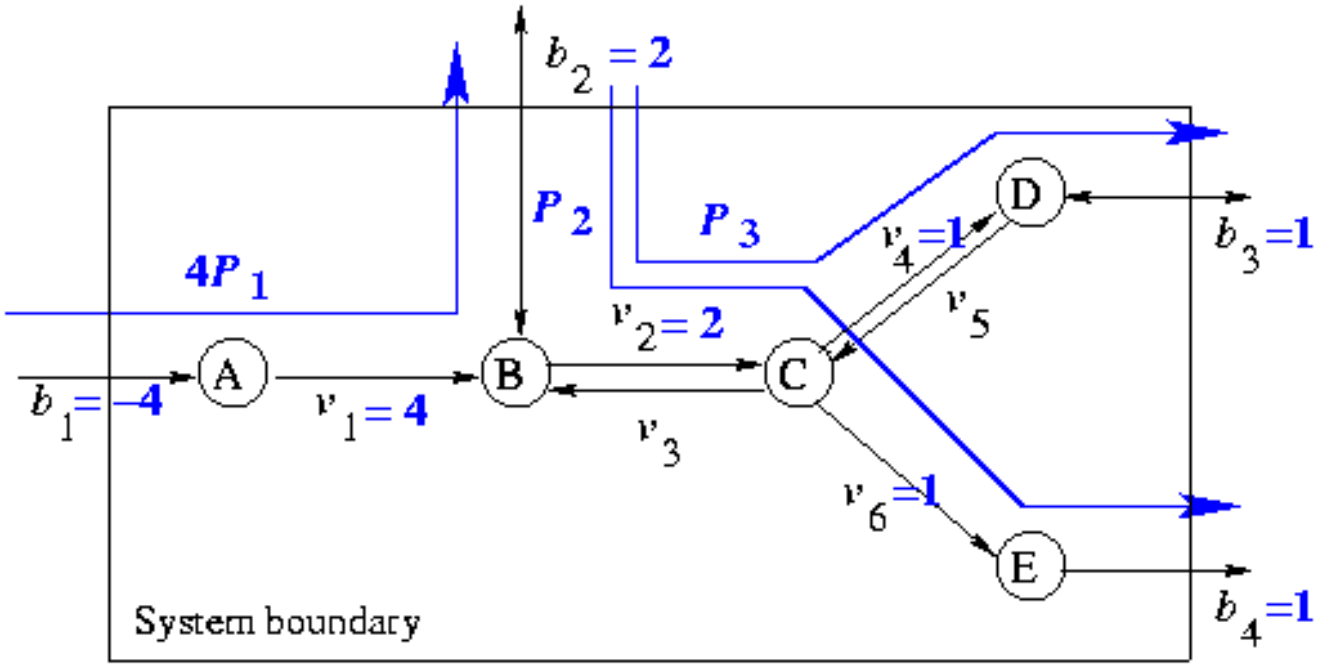
Some FBA Research

- Interior point solutions
  - New biology insights
  - Avoiding algorithm pitfalls
  - Sensitivity analysis from optimal partition
- Multiple objectives
  - New biology insights
  - Computing solutions
  - Visualizing solutions
- Pathway Regulation
  - MILP model
  - Implications for drug targeting
  - Empirical studies
- Sensitivity Analysis
  - FBA with LP: New insights from interior solutions
  - FBA/Regulations (MILP): what we can do

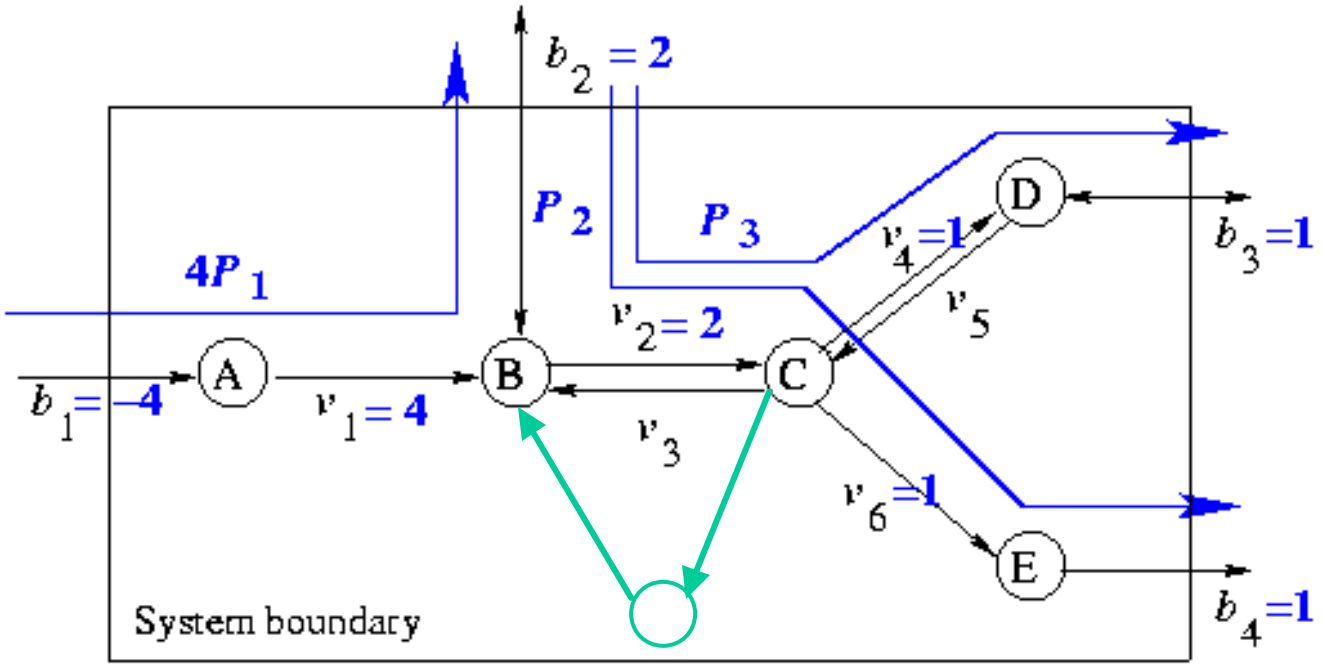
Interior Optimum for FBA

$v^* = 0 \Rightarrow v = 0$ in ***every*** optimum



Cycles

$v^*_7 = v^*_8 = v^*_2 > 0$ if cycle cost = 0



Optimization as a Phenotype Range Setter

$$\textbf{optimize } cv : \; Av = b, \; L \leq v \leq U$$

Objectives:

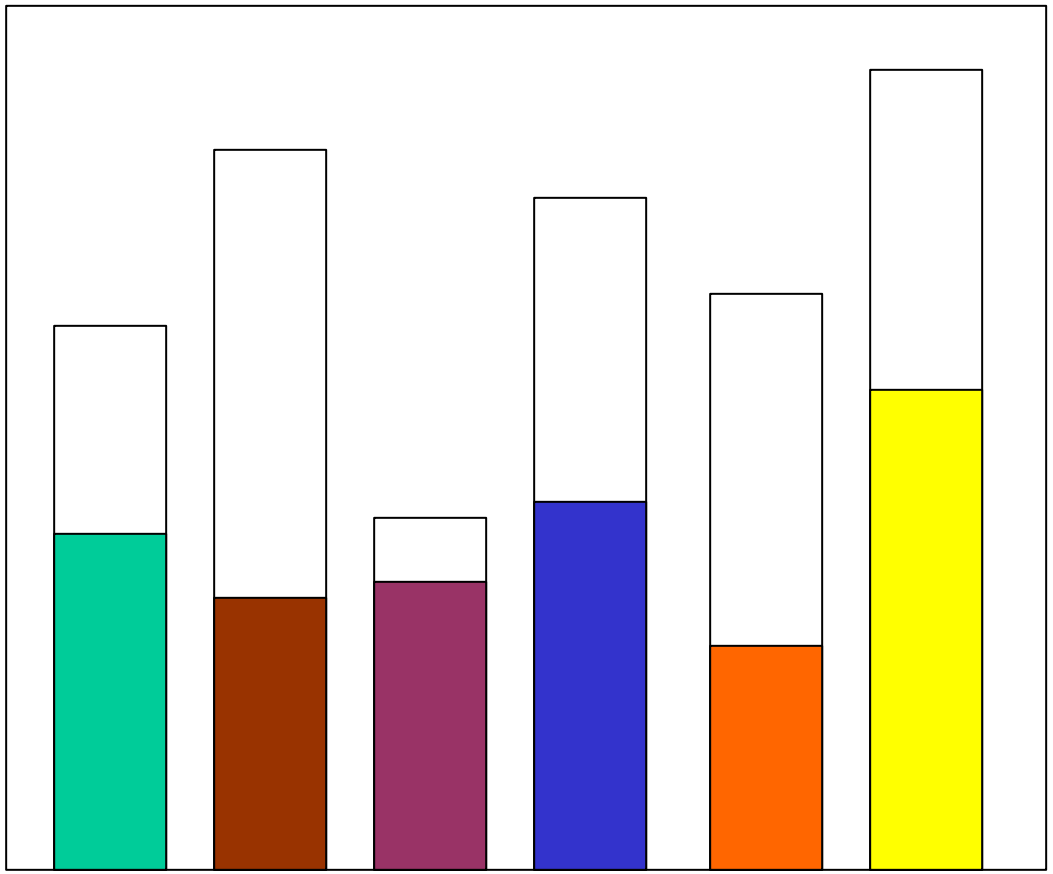
- **maximize growth flux**
- **maximize metabolite production (ATP)**
- **minimize by-product production**
- **minimize substrate requirements**
- **minimize mass nutrient uptake**

ref.: Palsson , Schilling, Schuster et al., 1992 – 2002

Optimization as a Complex Range Setter

optimize $\{c^1v, c^2v, \ldots, c^Mv\}$ **:** $Av = b,\ L \le v \le U$

Multiple Objectives



Optimization as a Filter

$$y_j = \begin{cases} 1 \text{ if } v_j > 0; \\ 0 \text{ if } v_j = 0. \end{cases}$$

minimize $\Sigma_j y_j$ **:** $Av = b,\ L_j y_j \le v_j \le y_j U_j$

Logical constraints:

exclusion ($v_j = 0$); inclusion ($v_j > 0$)

accomplished by $y_j = 0$ for j in E; $y_j = 1$ for j in I

conditional exclusion: do not use both reaction *k* and reaction *j*

accomplished by $y_k + y_j \le 1$

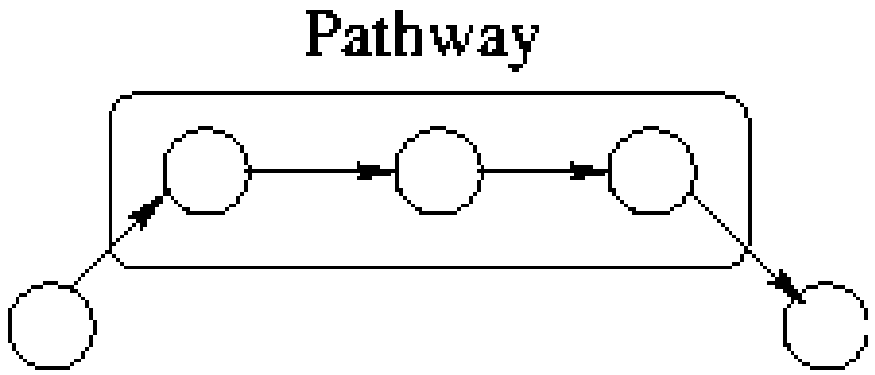
conditional inclusion: use reaction *k* or reaction *j*

accomplished by $y_k + y_j \ge 1$

Extends easily to other logical constraints over any set of reactions (or more complex processes)

Pathway Regulation

- **Multiple gene regulation**
- **Protein complex or family**



Turn off one member of pathway
(can choose, by some criteria)

Regulation MIP

$$y_{ij} = \begin{cases} \textbf{1 if gene } i \textbf{ assigned to regulate gene } j \\ \textbf{0 othewise.} \end{cases}$$

= 1 iff gene ***i*** can regulate gene ***j***

optimize $\sum c_{ij} y_{ij}$: $y_{ij} \in \{0, 1\}$

cover pathway *k*: $\sum_{j \in P_k} d_{ij} y_{ij} \geq 1$

gene *i* regulates at most 1 other gene: $\sum_j y_{ij} \leq 1$

Lots of opportunity for enhancements

- **Logical conditions (e.g., some combination of genes need to be on)**
- **Multiple gene regulators (complex cell signaling)**
- **Multiple criteria**
- **Goals & Penalties**
- ⋮

Agenda

- Talk about background
- Run some experiments
- Study results for biological significance
- Write papers
- Plan future collaborations
- Potential funding sources

Sessions

1. Convex sets & functions
2. Polyhedral computation
3. Sensitivity information from interior solutions in linear programming
4. Column generation
5. Multiple objectives
6. Projects revisited