Constraint-based models enable the study of metabolism at genome-scale

- M models: multiscale reconstructions of metabolism
- ME models include protein expression (even more multiscale)
- Stoichiometric matrix \( S \), fluxes \( v \), growth rate \( \mu \)
  - Most coefficients are moderate: \( S_{ij} = 0, \pm 1, \pm 2 \)
  - Some coefficients are large: \( S_{ij} = 10, 10^3 \)
- Similarly for fluxes because of coupling constraints: \( v_i/v_j \geq \mu / k_{\text{eff}} \Rightarrow v_i \leq (\mu / k_{\text{eff}}) v_j \)

Models are linear when \( \mu \) is fixed:

\[
\begin{align*}
\text{max} & \quad c^T v \\
\text{s.t} & \quad S v = b \\
& \quad v \geq 0 
\end{align*}
\]

Solved by:
- openCOBRA toolbox (CPLEX, glpk, Gurobi, MINOS, ...)
- MONGOOSE toolbox (exact simplex solver QSpOpt_ex)

### Linear ME model of \( E. coli \) double-MINOS, quad-MINOS LP

**Problem GlcAerWT (Thiele, Fleming, et al., 2012), 68300 \times 76664**

#### Step 1: double-MINOS, cold start, scaling

**Problem name** GlcAerWT EXIT — the problem is infeasible

- **No. of iterations**: 62856
- **Objective value**: -2.449880182E-04
- **No. of inequalities**: 41
- **No. of degenerate steps**: 33214
- **Percentage**: 52.84
- **Max \( c_\text{scaled} \)**: 1.0E-03
- **Max \( p \)**: 5000
- **Max Primal inf**: 134382.8E-02
- **Max Dual inf**: 97017.8E-05
- **Time for solving problem**: 97017.8 seconds

**Nonlinear ME model** variables \( \nu, v, w \)

- **\( \mu = \) growth rate**
- **A and \( B \) overlap**
- **\( st \ mu A v + B v = 0 \)**
- **\( st \ mu A v + w = 0 \)**
- **\( S v = b \)**
- **\( B v - w = 0 \)**
- **\( S v = b \)**
- **bounds on \( v \), none on \( w \)**

**Nonlinear ME model** quad-MINOS NLP

- **Penalty parameter**: 1.000000
- **Nonlinear objective**: 8.5566388920E-01
- **No. of calls to function**: 942
- **No. of calls to Hessian**: 942
- **No. of superbasics**: 0
- **Nonlinear constraints**: 1
- **Nonlinear objective**: 8.5566388920E-01
- **Nonlinear constraints**: 1

#### Step 2: quad-MINOS, warm start, scaling

**Problem name** GlcAerWT EXIT — optimal solution found

- **No. of iterations**: 53986
- **Objective value**: -7.0382449681E+05
- **Max Primal inf**: 134382.8E-02
- **Max Dual inf**: 97017.8E-05
- **Time for solving problem**: 3995.58 seconds

#### Step 3: quad-MINOS, warm start, no scaling

**Problem name** GlcAerWT EXIT — optimal solution found

- **No. of iterations**: 43
- **Objective value**: -7.0382449681E+05
- **Max Primal inf**: 134382.8E-02
- **Max Dual inf**: 97017.8E-05
- **Time for solving problem**: 97017.8 seconds

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