Constraint-based Modeling of Cellular Networks

Exercise 8 – ROOM

08. 12. 2022

ROOM

Step 1: FBA to find wild type flux distribution $\boldsymbol{w}$

$$\max c^T w$$

$$s.t.$$

$$Nw = 0$$

$$w_{min} \le w \le w_{max}$$

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Step 2: Determine the significance thresholds for the flux changes ($\boldsymbol{w^u}$ and $\boldsymbol{w^l}$).

$\boldsymbol{\delta = 0.05}$ **and** $\boldsymbol{\varepsilon = 0.001}$

for $1 \leq i \leq r$ → r being the number of reactions

$w_i^u = w_i + \delta|w_i| + \varepsilon$

$w_i^l = w_i - \delta|w_i| - \varepsilon$

Q: What is the dimension of w^u and w^l?

ROOM

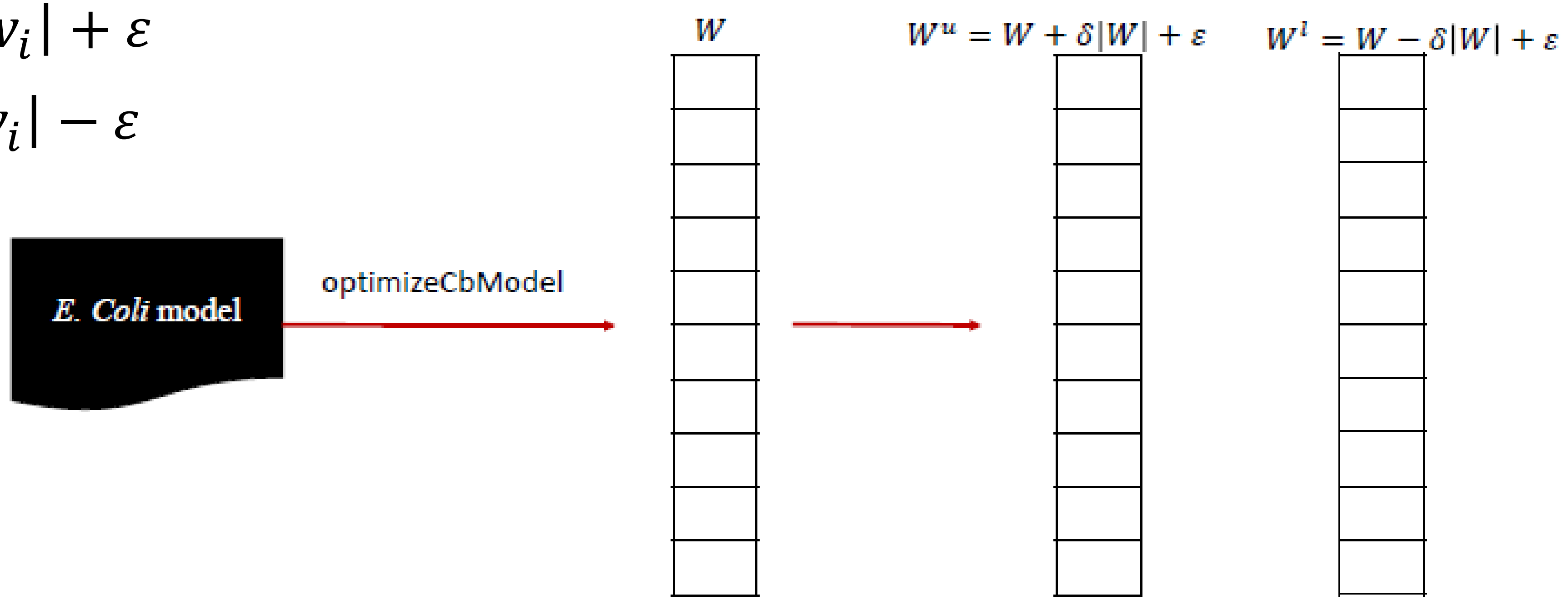
Step 2: Determine the significance thresholds for the flux changes (w^u and w^l).

$\delta = 0.05$ and $\varepsilon = 0.001$

for $1 \leq i \leq r$ → r being the number of reactions

$$w_i^u = w_i + \delta|w_i| + \varepsilon$$

$$w_i^l = w_i - \delta|w_i| - \varepsilon$$



ROOM

Step 3: Put inequality constraints in a matrix form for the optimization problem.

Q: What are the variables, we try to estimate?

for $1 \leq i \leq r$

$$v_i - y_i(v_{max,i} - w_i^u) \leq w_i^u$$

$$v_i - y_i(v_{min,i} - w_i^l) \geq w_i^l$$

ROOM

Step 3: Put inequality constraints in a matrix form for the optimization problem.

Here the variables for the optimization problem are the vectors of v and y.

for $1 \leq i \leq r$

$$v_i - y_i(v_{max,i} - w_i^u) \leq w_i^u$$

$$v_i - y_i(v_{min,i} - w_i^l) \geq w_i^l$$

variable vector

$$\begin{bmatrix} v_1 \\ \vdots \\ v_r \\ y_1 \\ \vdots \\ y_r \end{bmatrix}$$

ROOM

Step 3: Put inequality constraints in a matrix form for the optimization problem.

Here the variables for the optimization problem are the vectors of v and y.

for $1 \le i \le r$

$v_i - y_i(v_{max,i} - w_i^u) \le w_i^u$

$$
\begin{array}{cc}
 & \begin{array}{cccccc} v_1 & \cdots & v_r & y_1 & \cdots & y_r \end{array} \\
\begin{array}{c} i=1 \\ \cdots \\ i=r \end{array} & \begin{bmatrix} 1 & 0 & 0 & -(v_{max,1} - w_1^u) & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & -(v_{max,r} - w_r^u) \end{bmatrix}
\end{array}
\cdot
\begin{array}{c} v_1 \\ \cdots \\ v_r \\ y_1 \\ \cdots \\ y_r \end{array}
\le w_i^u
$$

ROOM

Step 3: Put inequality constraints in a matrix form for the optimization problem.

Here the variables for the optimization problem are the vectors of v and y.

for $1 \le i \le r$

$$v_i - y_i(v_{max,i} - w_i^u) \le w_i^u$$

Implement it simmilarly for
$v_i - y_i\left(v_{min,i} - w_i^l\right) \ge w_i^l$

$$\begin{array}{c} \\ i=1 \\ \cdots \\ i=r \end{array}\begin{array}{c} \begin{array}{cccccc} v_1 & \cdots & v_r & y_1 & \cdots & y_r \end{array} \\ \begin{bmatrix} 1 & 0 & 0 & -(v_{max,1} - w_1^u) & 0 & 0 \\ & & & & & \\ 0 & 0 & 1 & 0 & 0 & -(v_{max,r} - w_r^u) \end{bmatrix} \end{array} \cdot \begin{array}{c} v_1 \\ \cdots \\ v_r \\ y_1 \\ \cdots \\ y_r \end{array} \le w_i^u$$

ROOM

$$\min_{y,v} \sum_{i=1}^{r} y_i$$

s.t

$$Sv = 0,\ v_{min} \le v \le v_{max}$$

$$v_j = 0, for\ \forall j\ blocked\ by\ gene\ knock - out$$

for $1 \le i \le r$

$$v_i - y_i\left(v_{max,i} - w_i^u\right) \le w_i^u$$

$$v_i - y_i(v_{min,i} - w_i^l) \ge w_i^l$$

$$y_i \in \{0,1\}$$

ROOM

$$\min_{y,v} \sum_{i=1}^{r} y_i$$

s.t

$$Nv = 0,\ v_{min} \le v \le v_{max}$$

$$v_j = 0, for\ \forall j\ blocked\ by\ gene\ knock-out$$

for $1 \le i \le r$

$$v_i - y_i\left(v_{max,i} - w_i^u\right) \le w_i^u$$

$$v_i - y_i\left(v_{min,i} - w_i^l\right) \ge w_i^l$$

$$y_i \in \{0,1\}$$

$$\begin{array}{c} v_1 \quad \dots \quad v_r \quad y_1 \quad \dots \quad y_r \\ \begin{bmatrix} \mathbf{N} & \begin{matrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{matrix} \end{bmatrix} \end{array} \cdot \begin{matrix} v_1 \\ \dots \\ v_r \\ y_1 \\ \dots \\ y_r \end{matrix} = 0$$

$$\begin{array}{c|cccccc} & v_1 & \dots & v_r & y_1 & \dots & y_r \\ i=1 & 1 & 0 & 0 & -(v_{max,1} - w_1^u) & 0 & 0 \\ \dots & & & & & & \\ i=r & 0 & 0 & 1 & 0 & 0 & -(v_{max,r} - w_r^u) \end{array} \cdot \begin{matrix} v_1 \\ \dots \\ v_r \\ y_1 \\ \dots \\ y_r \end{matrix} \le w_i^u$$

$$\begin{array}{c|cccccc} i=1 & 1 & 0 & 0 & -(v_{min,1} - w_1^l) & 0 & 0 \\ \dots & & & & & & \\ i=r & 0 & 0 & 1 & 0 & 0 & -(v_{min,r} - w_r^l) \end{array} \cdot \begin{matrix} v_1 \\ \dots \\ v_r \\ y_1 \\ \dots \\ y_r \end{matrix} \ge w_i^u$$

ROOM

$$\begin{array}{c} \begin{array}{cccccc} v_1 & \dots & v_r & y_1 & \dots & y_r \end{array} \\ \left[\begin{array}{cccc} S & 0 & 0 & 0 \\ & 0 & 0 & 0 \\ & 0 & 0 & 0 \end{array} \right] \cdot \begin{bmatrix} v_1 \\ \dots \\ v_r \\ y_1 \\ \dots \\ y_r \end{bmatrix} = 0 \end{array}$$

$$\begin{array}{c|cccccc} & v_1 & \dots & v_r & y_1 & \dots & y_r \\ i = 1 & 1 & 0 & 0 & -(v_{max,1} - w_1^u) & 0 & 0 \\ \dots & & & & & & \\ i = r & 0 & 0 & 1 & 0 & 0 & -(v_{max,r} - w_r^u) \end{array} \cdot \begin{bmatrix} v_1 \\ \dots \\ v_r \\ y_1 \\ \dots \\ y_r \end{bmatrix} \leq w_i^u$$

$$\begin{array}{c|cccccc} i = 1 & 1 & 0 & 0 & -(v_{min,1} - w_1^l) & 0 & 0 \\ \dots & & & & & & \\ i = r & 0 & 0 & 1 & 0 & 0 & -(v_{min,r} - w_r^l) \end{array} \cdot \begin{bmatrix} v_1 \\ \dots \\ v_r \\ y_1 \\ \dots \\ y_r \end{bmatrix} \geq w_i^l$$

$$\min_{y,v} \sum_{i=1}^{r} y_i$$

s.t

$$Nv = 0, \; v_{min} \leq v \leq v_{max}$$

$$v_j = 0, for\ \forall j\ blocked\ by\ gene\ knock-out$$

for $1 \leq i \leq r$

$$v_i - y_i\left(v_{max,i} - w_i^u\right) \leq w_i^u$$
$$v_i - y_i\left(v_{min,i} - w_i^l\right) \geq w_i^l$$
$$\boldsymbol{y_i \in \{0,1\}}$$

MILP problem!

Use intlinprog() to solve

```
intlinprog Mixed integer linear programming.

   X = intlinprog(f,intcon,A,b) attempts to solve problems of the form

            min f'*x    subject to:  A*x  <= b
             x                       Aeq*x = beq
                                     lb <= x <= ub
                                     x(i) integer, where i is in the index
                                     vector intcon (integer constraints)

   X = intlinprog(f,intcon,A,b) solves the problem with integer variables
   in the intcon vector and linear inequality constraints A*x <= b. intcon
   is a vector of positive integers indicating components of the solution
   X that must be integers. For example, if you want to constrain X(2) and
   X(10) to be integers, set intcon to [2,10].

   X = intlinprog(f,intcon,A,b,Aeq,beq) solves the problem above while
   additionally satisfying the equality constraints Aeq*x = beq. (Set A=[]
   and b=[] if no inequalities exist.)

   X = intlinprog(f,intcon,A,b,Aeq,beq,LB,UB) defines a set of lower and
   upper bounds on the design variables, X, so that the solution is in the
   range LB <= X <= UB. Use empty matrices for LB and UB if no bounds
   exist. Set LB(i) = -Inf if X(i) is unbounded below; set UB(i) = Inf if
   X(i) is unbounded above.
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How to find reactions associated with a gene?

Use the GPR rules in the model structure to find related genes

Use model field rxnGeneMat

You can also check the Cobra Toolbox function *findRxnsFromGenes*

$$\min_{y,v} \sum_{i=1}^{r} y_i$$

s.t

$$Nv = 0,\ v_{min} \leq v \leq v_{max}$$

$$v_j = 0, for\ \forall j\ blocked\ by\ gene\ knock-out$$

$$\text{for } 1 \leq i \leq r$$

$$v_i - y_i(v_{max,i} - w_i^u) \leq w_i^u$$
$$v_i - y_i(v_{min,i} - w_i^l) \geq w_i^l$$
$$y_i \in \{0,1\}$$