Constraint-based Modeling of Cellular Networks

Exercise 10 – OptReg

5. 1. 2023

Implementation of simplified OptReg

As last week:

- Set the lower bound of ‘Fumarase’ (FUM) and ‘ATP maintenance requirement’ reaction to zero.
- Calculate the optimum biomass flux z^*, under the steady state constraints.
- Calculate the optimum flux through fumarase reaction w_FUM, under steady state constraints at the optimum biomass.
- Split reversible reactions in the model into two irreversible reactions.

Simplified OptReg

Use *flux variability analysis (FVA)* to find the minimum and maximum values for all reaction fluxes, while

(1) having no constraint on biomass production (v^{min} and v^{max})

(2) fixing the biomass reaction flux to the maximum biomass (v^L and v^U)

$$\boxed{\begin{gathered} v^{min}/v^{max} = min\ /\max v_i \\ \mathrm{Nv} = 0 \\ lb \leq v \leq ub \end{gathered} \qquad (1)}$$

$$\boxed{\begin{gathered} v^{L}/v^{U} = min\ /\max v_i \\ \mathrm{Nv} = 0 \\ v_{bio} = v_{bio}^{max} \\ lb \leq v \leq ub \end{gathered} \qquad (2)}$$

Simplified OptReg

Use *flux variability analysis (FVA)* to find the minimum and maximum values for all reaction fluxes, while

(1) having no constraint on biomass production (v^{min} and v^{max})

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$$\begin{gathered} v^{min}/v^{max} = min\ /\max v_i \\ \mathrm{Nv} = 0 \\ lb \leq v \leq ub \end{gathered} \tag{1}$$

$$\begin{gathered} v^{L}/v^{U} = min\ /\max v_i \\ \mathrm{Nv} = 0 \\ v_{bio} = v_{bio}^{max} \\ lb \leq v \leq ub \end{gathered} \tag{2}$$

Having at least 90% of the maximum biomass in the *E. coli* model, flux through fumarase reaction should be increased by 70%

$$v_{bio} \geq 0.9 \cdot v_{bio}^{max}$$

$$v_{FUM} \geq 1.7 \cdot v_{FUM}^{U}$$

Simplified OptReg

For each reaction, there are three modifications

$$\begin{cases} \text{Knock-out } (y^k) \\ \text{Up-regulation } (y^u) \\ \text{Down-regulation } (y^d) \end{cases}$$

$$\varepsilon y_i^k \leq v_i$$
$$v_i \leq v_i^{max} y_i^k + (1 - y_i^k)\varepsilon$$

$$v_i^{min} y_i^u + \left(v_i^U (1 - C) + v_i^{max} C\right)(1 - y_i^u) \leq v_i$$
$$v_i \leq v_i^{max}(1 - y_i^u) + v_i^U y_i^u$$

$$v_i^{min}\left(1 - y_i^d\right) + v_i^L y_i^d \leq v_i$$
$$v_i \leq \left(v_i^L (1 - C) + v_i^{min} C\right)(1 - y_i^d) + v_i^{max} y_i^d$$

$$y^d, y^u, y^k \in \{0,1\}$$

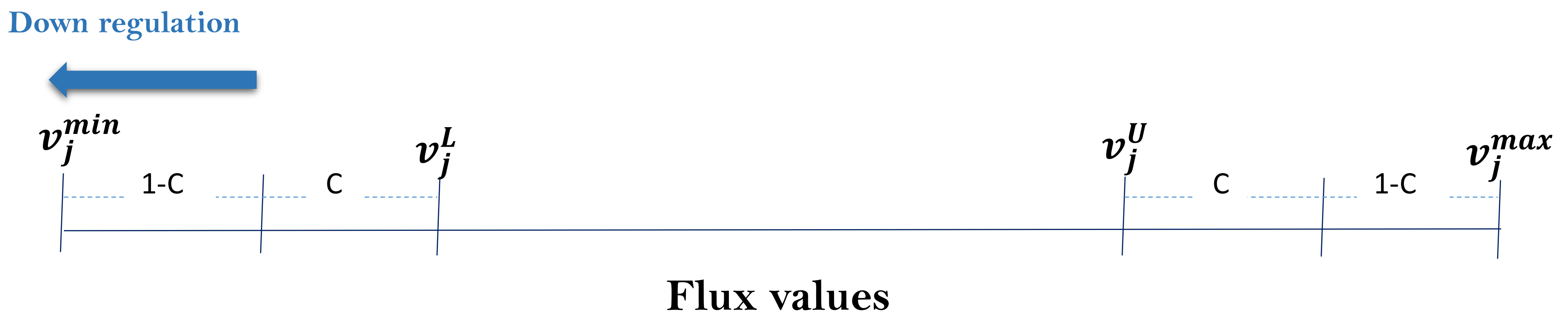
$$C = 0.001$$
$$\varepsilon = 1e - 6$$

Simplified OptReg

For each reaction, there are three modifications $\begin{cases} \text{Knock-out } (y^k) \\ \text{Up-regulation } (y^u) \\ \text{Down-regulation } (y^d) \end{cases}$

$$y_j^d = \begin{cases} 0 & \textit{if reaction i is downregulated} \\ 1 & \textit{if reaction i is unchanged} \end{cases}$$

$$\begin{cases} v_j^{min}(1-y_j^d) + v_j^L \cdot y_j^d \le v_j & \text{LB} \\ v_j \le \left(v_j^L(1-C) + v_j^{min} \cdot C\right)(1-y_j^d) + v_j^{max} y_j^d & \text{UB} \end{cases}$$



Simplified OptReg

For each reaction, there are three modifications

- Knock-out (y^k)
- Up-regulation (y^u)
- Down-regulation (y^d)

$$y_j^d = \begin{cases} 0 & \text{if reaction } i \text{ is downregulated} \\ 1 & \text{if reaction } i \text{ is unchanged} \end{cases}$$

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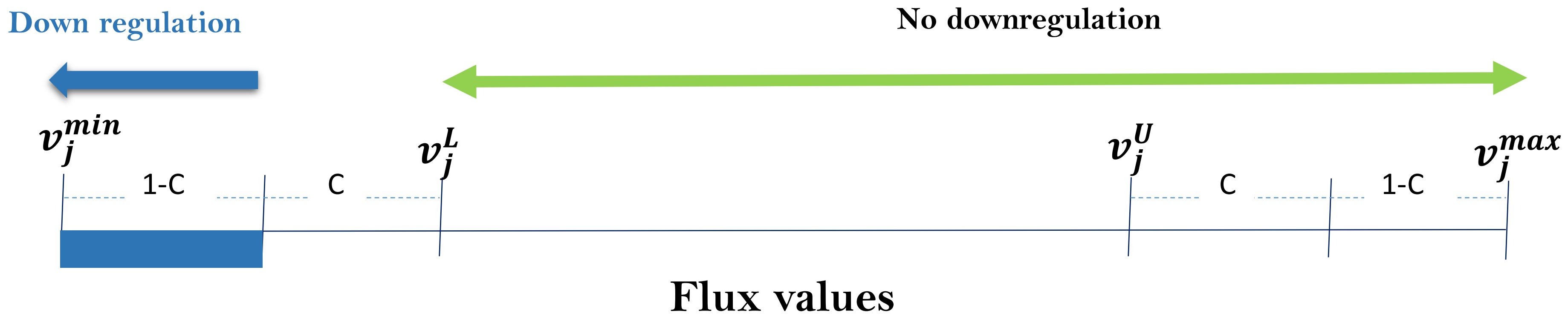

Simplified OptReg

For each reaction, there are three modifications

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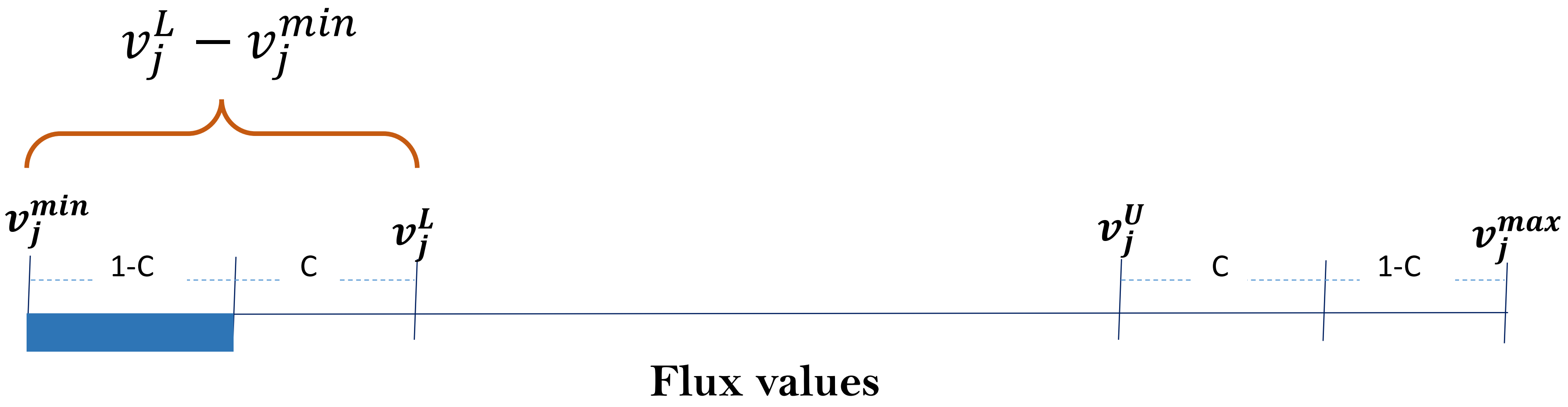

Simplified OptReg

For each reaction, there are three modifications
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$$y_j^d = \begin{cases} 0 & \textit{if reaction i is downregulated} \\ 1 & \textit{if reaction i is unchanged} \end{cases}$$

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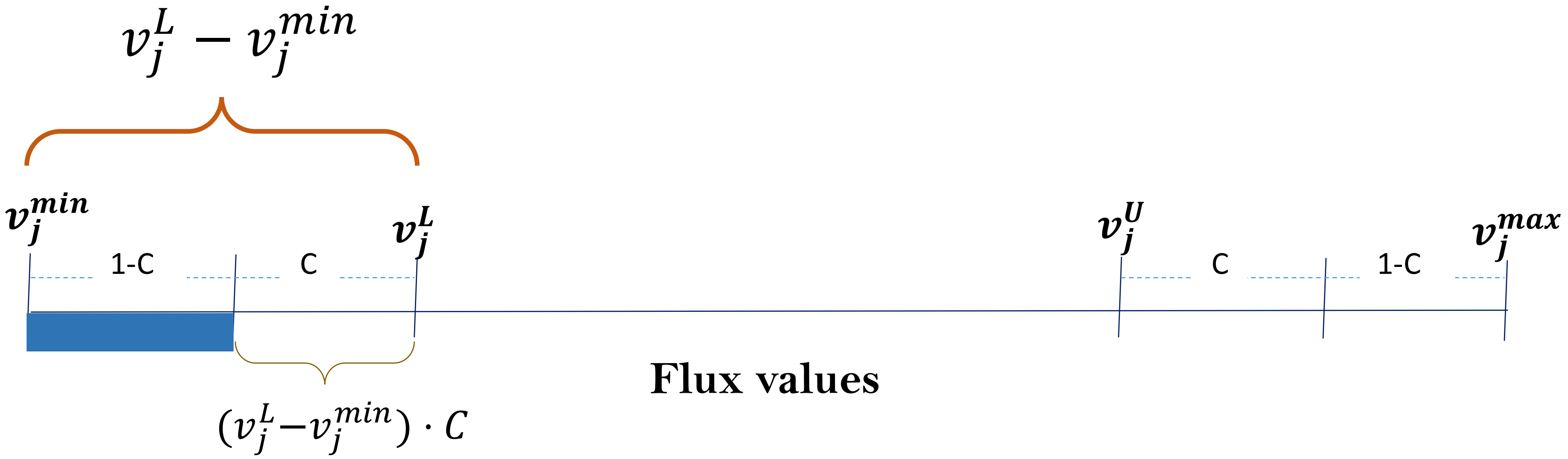

Simplified OptReg

For each reaction, there are three modifications

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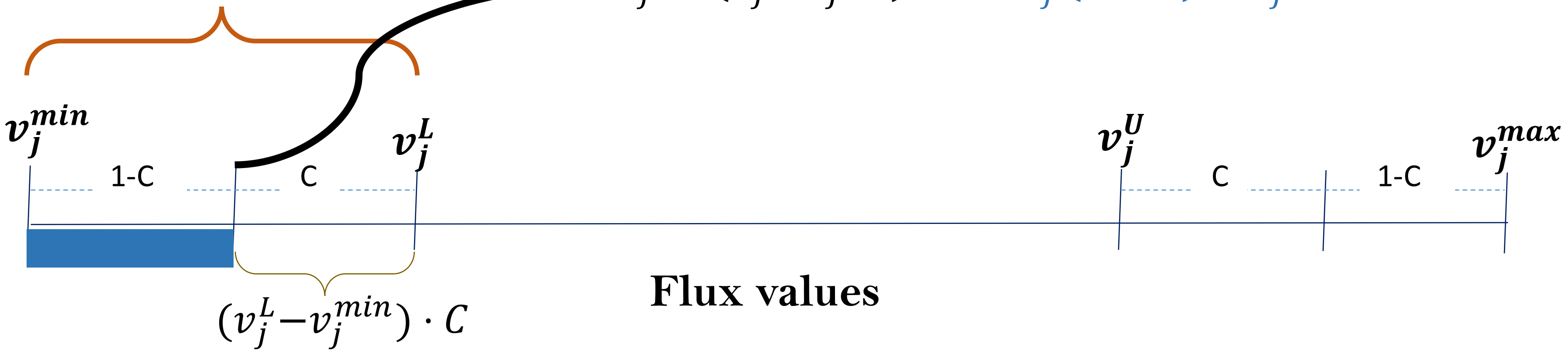
$$v_j^L - v_j^{min}$$

$$v_j^L - (v_j^L - v_j^{min}) \cdot C = v_j^L(1 - C) + v_j^{min} \cdot C$$



Simplified OptReg

For each reaction, there are three modifications $\begin{cases} \text{Knock-out } (y^k) \\ \text{Up-regulation } (y^u) \\ \text{Down-regulation } (y^d) \end{cases}$

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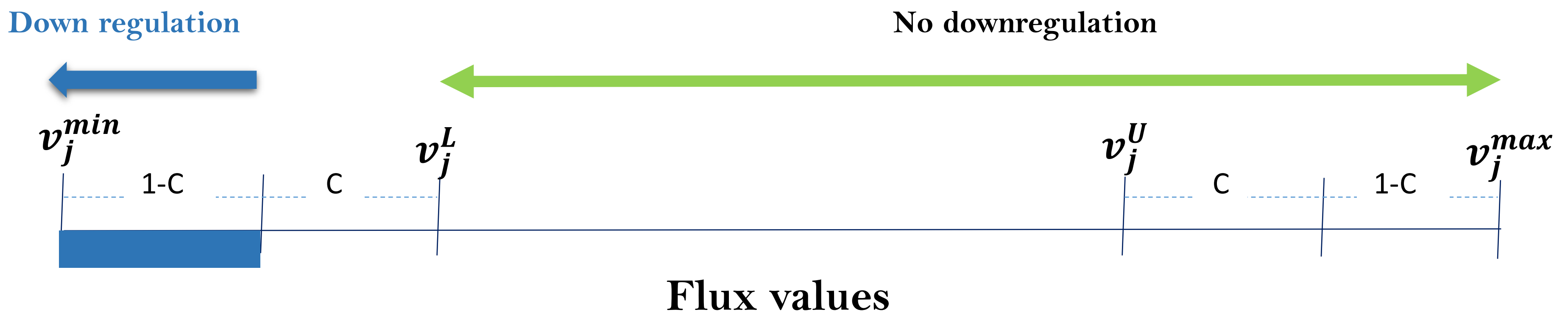

Simplified OptReg

We allow a single type of genetic manipulation (y_i^u up-regulation, y_i^d down-regulation, y_i^k knock-out) per reaction

$$(1 - y_i^u) + (1 - y_i^d) + (1 - y_i^k) \leq 1$$

For reversible reactions j add the following constraints:

$y_j^k = y_{j+1}^k$ (both directions have to be knocked-out)
$y_j^u + y_{j+1}^u \geq 1$ (only one direction up-regulated
$y_j^d + y_{j+1}^d \geq 1$ or down-regulated)

y_j^u denotes the integer variable associated with the forward reaction
y_{j+1}^u is the integer associated with the respective backward reaction

Alternative Solution – integer cut

- In the first solution find which integer variables are zero

  e.g. We find $y_{51}^{d} and\ y_{3}^{u}$ to be zero

- Add an additional constraint:

  $y_{51}^{d} + y_{3}^{u} \geq 1$

  At least one of it has to be one and hence is not modified in the alternative solution