(P4) Mixed Integer Linear model for route selection

Objective function

$$\min \ \text{cost} = \sum_{j \in E^1} \mathbf{v_j^1} + \sum_{j \in (E^2 \cup E^3)} \left[\mathbf{v_j^1} + \mathbf{v_j^3}\right] + \sum_{j \in (E^{2'} \cup E^3)} \mathbf{v_j^2} \tag{1}$$

Restrictions

Batch stages

$$\mathbf{y_j^1} + \mathbf{x_j^1} \geq \mathbf{z_{ih}^1} s_{ihj}^1 + \mathbf{y_i^4} \qquad \forall i \in I, j \in E^1 \tag{2}$$

$$\mathbf{y_i^5} + \mathbf{x_j^2} \geq \mathbf{z_{ih}^1} t_{ihj}^0 \qquad \forall i \in I, j \in E^1 \tag{3}$$

Semi-continuous stages

$$\mathbf{y_j^1} \geq \mathbf{z_{ih}^1} s_{ihj}^1 + \mathbf{y_i^4} \qquad \forall i \in I, j \in E^2 \tag{4}$$

$$\mathbf{y_j^2} \geq \mathbf{z_{ih}^1} s_{ihj}^2 + \mathbf{y_i^4} \qquad \forall i \in I, j \in E^{2'} \tag{5}$$

$$\mathbf{y_i^5} + \mathbf{x_j^2} \geq \mathbf{z_{ih}^1} t_{ihj}^1 + \mathbf{y_i^4} - \mathbf{x_j^1} - \mathbf{y_j^3} \qquad \forall i \in I, j \in E^2 \tag{6}$$

Chromatographic stages

$$\mathbf{y_j^1} \geq \mathbf{z_{ih}^1} s_{ihj}^1 + \mathbf{y_i^4} \qquad \forall i \in I, j \in E^3 \tag{7}$$

$$\mathbf{y_j^2} \geq \mathbf{z_{ih}^1} s_{ihj}^2 + \mathbf{y_i^4} \qquad \forall i \in I, j \in E^3 \tag{8}$$

$$\mathbf{y_j^3} + \mathbf{x_j^1} \geq \mathbf{z_{ih}^1} s_{ihj}^3 + \mathbf{y_i^4} \qquad \forall i \in I, j \in E^3 \tag{9}$$

$$\mathbf{y_i^5} + \mathbf{x_j^2} \geq \alpha_{ijk}^6 \left(\mathbf{y_i^4} - \mathbf{x_j^1} - \mathbf{y_j^3}\right) - \mathbf{z_{ih}^1} \alpha_{ijk}^6 b_{ijk}^6 + \mathbf{z_{ih}^1} \beta_{ijk}^6 \qquad \forall i \in I, j \in (E^3 \setminus E^{3'}), k \in K^{6'} \tag{10}$$

$$\mathbf{y_i^5} + \mathbf{x_j^2} \geq \mathbf{z_{ih}^1} t_{ihj}^0 \qquad \forall i \in I, j \in E^{3'} \tag{11}$$

Planning horizon

$$\sum_{i \in I} \mathbf{v_i^7} \leq 1 + \mathbf{r} \tag{12}$$

$$\mathbf{v_i^7} \geq \alpha_{ik}^7 \left(\mathbf{y_i^5} - \mathbf{y_i^4}\right) - \mathbf{z_{ih}^1} \alpha_{ik}^7 b_{ik}^7 + \mathbf{z_{ih}^1} \beta_{ik}^7 \qquad \forall i \in I, k \in K^{7'} \tag{13}$$

Binary variables for duplication of units

$$\mathbf{x_j^1} = \sum_{k \in K} \mathbf{y_{jk}^6} \ln(k) \qquad \forall j \in E \tag{14}$$

$$\sum_{k \in K} \mathbf{y_{jk}^6} = \mathbf{z_j^2} \qquad \forall j \in E \tag{15}$$

$$\mathbf{x_j^2} = \sum_{k \in K} \mathbf{y_{jk}^7} \ln(k) \qquad \forall j \in E \tag{16}$$

$$\sum_{k \in K} \mathbf{y_{jk}^7} = \mathbf{z_j^2} \qquad \forall j \in E \tag{17}$$

Binary variables for selection of hosts and stages

$$\sum_{(i,h) \in I \times H} \mathbf{z_{ih}^1} \leq 1 \tag{18}$$

$$\mathbf{z_{ih}^1} \leq \mathbf{z_j^2} \qquad \forall (i,h,j) \in R \tag{19}$$

Auxiliary variables

$$\mathbf{v_j^1} \geq \alpha_{jk}^1 \left(\mathbf{x_j^1} + \mathbf{x_j^2} + \gamma_j^1 \mathbf{y_j^1}\right) - \mathbf{z_j^2} \alpha_{jk}^1 b_{jk}^1 + \mathbf{z_j^2} \beta_{jk}^1 \qquad \forall j \in E^1, k \in K^{1'} \tag{20}$$

$$\mathbf{v_j^1} \geq \alpha_{jk}^1 \left(\mathbf{x_j^2} + \gamma_j^1 \mathbf{y_j^1}\right) - \mathbf{z_j^2} \alpha_{jk}^1 b_{jk}^1 + \mathbf{z_j^2} \beta_{jk}^1 \qquad \forall j \in (E^2 \cup E^3), k \in K^{1'} \tag{21}$$

$$\mathbf{v_j^2} \geq \alpha_{jk}^2 \left(\mathbf{x_j^2} + \gamma_j^2 \mathbf{y_j^2}\right) - \mathbf{z_j^2} \alpha_{jk}^2 b_{jk}^2 + \mathbf{z_j^2} \beta_{jk}^2 \qquad \forall j \in (E^{2'} \cup E^3), k \in K^{2'} \tag{22}$$

$$\mathbf{v_j^3} \geq \alpha_{jk}^3 \left(\mathbf{x_j^2} + \gamma_j^3 \mathbf{y_j^3}\right) - \mathbf{z_j^2} \alpha_{jk}^3 b_{jk}^3 + \mathbf{z_j^2} \beta_{jk}^3 \qquad \forall j \in E^3, k \in K^{3'} \tag{23}$$

Variable bounds Each variable has upper and lower bounds set by the user.

$$y_j^{1,lo} \mathbf{z_j^2} \leq \mathbf{y_j^1} \leq y_j^{1,up} \mathbf{z_j^2} \qquad \forall j \in E^1 \tag{24}$$

$$y_j^{2,lo} \mathbf{z_j^2} \leq \mathbf{y_j^2} \leq y_j^{2,up} \mathbf{z_j^2} \qquad \forall j \in (E^{2'} \cup E^3) \tag{25}$$

$$y_j^{3,lo} \mathbf{z_j^2} \leq \mathbf{y_j^3} \leq y_j^{3,up} \mathbf{z_j^2} \qquad \forall j \in (E^2 \cup E^3) \tag{26}$$

$$x_j^{1,lo} \mathbf{z_j^2} \leq \mathbf{x_j^1} \leq x_j^{1,up} \mathbf{z_j^2} \qquad \forall j \in E \tag{27}$$

$$x_j^{2,lo} \mathbf{z_j^2} \leq \mathbf{x_j^2} \leq x_j^{2,up} \mathbf{z_j^2} \qquad \forall j \in E \tag{28}$$

$$y_{ih}^{4,lo}\mathbf{z_{ih}^1} \leq \mathbf{y_{ih}^4} \leq y_{ih}^{4,up}\mathbf{z_{ih}^1} \qquad \forall (i,h) \in I \times H \tag{29}$$

$$y_{ih}^{5,lo}\mathbf{z_{ih}^1} \leq \mathbf{y_{ih}^5} \leq y_{ih}^{5,up}\mathbf{z_{ih}^1} \qquad \forall (i,h) \in I \times H \tag{30}$$

$$\mathbf{v_j^1} \leq c_j^1 \exp\left(x_j^{1,up} + x_j^{2,up} + \gamma_j^1 y_j^{1,up}\right)\mathbf{z_j^2} \qquad \forall j \in E^1 \tag{31}$$

$$\mathbf{v_j^1} \leq c_j^1 \exp\left(x_j^{2,up} + \gamma_j^1 y_j^{1,up}\right)\mathbf{z_j^2} \qquad \forall j \in (E^2 \cup E^3) \tag{32}$$

$$\mathbf{v_j^2} \leq c_j^2 \exp\left(x_j^{2,up} + \gamma_j^2 y_j^{2,up}\right)\mathbf{z_j^2} \qquad \forall j \in (E^{2'} \cup E^3) \tag{33}$$

$$\mathbf{v_j^3} \leq c_j^3 \exp\left(x_j^{1,up} + x_j^{2,up} + \gamma_j^3 y_j^{3,up}\right)\mathbf{z_j^2} \qquad \forall j \in (E^2 \cup E^3) \tag{34}$$

$$\mathbf{v_{ih}^7} \leq \exp\left(\min\left[y_{ih}^{5,up} - y_{ih}^{4,lo}, \ln(\delta) - \ln(d_i)\right] + \ln(d_i) - \ln(\delta)\right)\mathbf{z_{ih}^1} \qquad \forall (i,h) \in I \times H \tag{35}$$

Using constraints (2) to (10) we can refine y_i^4 upper bound and y_i^5 lower bound.

$$\begin{aligned} y_i^{4,up} = \min\Bigg[&\min_{(i,h,j)\in I\times H\times E^1}\left(y_j^{1,up} + x_j^{1,up} - s_{ihj}^1\right), \min_{(i,h,j)\in I\times H\times (E^2\cup E^3)}\left(y_j^{1,up} - s_{ihj}^1\right), \\ &\min_{(i,h,j)\in I\times H\times (E^{2'}\cup E^3)}\left(y_j^{2,up} - s_{ihj}^2\right), \min_{(i,h,j)\in I\times H\times E^3}\left(y_j^{3,up} + x_j^{1,up} - s_{ihj}^3\right)\Bigg] \end{aligned} \tag{36}$$

$$\begin{aligned} y_i^{5,lo} = \max\Bigg[&\max_{(i,h,j)\in I\times H\times (E^1\cup E^{3'})}\left(t_{ihj}^0 - x_j^{2,up}\right), \\ &\max_{(i,h,j)\in I\times H\times (E^3\setminus E^{3'})}\left(\ln\left(T_{ihj}^0 + \exp\left(t_{ihj}^1 - y_j^{3,up} - x_j^{1,up}\right)\right) - x_j^{2,up}\right)\Bigg] \end{aligned} \tag{37}$$

Parameters for linear approximations with equispaced cutting points

$$a_j^1 = \frac{v_j^{1,up} - v_j^{1,lo}}{NK1} \qquad \forall j \in U^1 \tag{38}$$

$$a_j^2 = \frac{v_j^{2,up} - v_j^{2,lo}}{NK2} \qquad \forall j \in U^2 \tag{39}$$

$$a_j^3 = \frac{v_j^{3,up} - v_j^{3,lo}}{NK3} \qquad \forall j \in U^3 \tag{40}$$

$$a_{ihj}^6 = \frac{z_{ihj}^{6,up} - z_{ihj}^{6,lo}}{NK6} \qquad \forall (i,h,j) \in I \times H \times (E^3 \setminus E^{3'}) \tag{41}$$

$$a^7_{ih} = \frac{z^{7,up}_{ih} - z^{7,lo}_{ih}}{NK7} \qquad \forall (i,h) \in I \times H \tag{42}$$

$$b^1_{jk} = v^{1,lo}_j + (k-1)a^1_j \qquad \forall j \in U^1, k \in K^{1'} \tag{43}$$

$$b^2_{jk} = v^{2,lo}_j + (k-1)a^2_j \qquad \forall j \in U^2, k \in K^{2'} \tag{44}$$

$$b^3_{jk} = v^{3,lo}_j + (k-1)a^3_j \qquad \forall j \in U^3, k \in K^{3'} \tag{45}$$

$$b^6_{ihjk} = z^{6,lo}_{ihj} + (k-1)a^6_{ihj} \qquad \forall (i,h,j) \in I \times H \times (E^3 \setminus E^{3'}) \tag{46}$$

$$b^7_{ihk} = z^{7,lo}_{ih} + (k-1)a^7_{ih} \qquad \forall (i,h) \in I \times H, k \in K^{7'} \tag{47}$$

$$\beta^1_{jk} = c^1_j \exp(b^1_{jk}) \qquad \forall j \in U^1, k \in K^{1'} \tag{48}$$

$$\beta^2_{jk} = c^2_j \exp(b^2_{jk}) \qquad \forall j \in U^2, k \in K^{2'} \tag{49}$$

$$\beta^3_{jk} = c^3_j \exp(b^3_{jk}) \qquad \forall j \in U^3, k \in K^{3'} \tag{50}$$

$$\beta^6_{ihjk} = \ln(T^0_{ihj} + \exp(t^1_{ihj} + b^6_{ihjk})) \qquad \forall (i,h,j) \in I \times H \times (E^3 \setminus E^{3'}) \tag{51}$$

$$\beta^7_{ihk} = \exp(b^7_{ihk} + \ln(d_i) - \ln(\delta)) \qquad \forall (i,h) \in I \times H, k \in K^{7'} \tag{52}$$

$\boldsymbol{\alpha}$ values for lower approximations

$$\alpha^1_{jk} = c^1_j \exp(b^1_{jk}) \qquad \forall j \in U^1, k \in K^{1'} \tag{53}$$

$$\alpha^2_{jk} = c^2_j \exp(b^2_{k}) \qquad \forall j \in U^2, k \in K^{2'} \tag{54}$$

$$\alpha^3_{jk} = c^3_j \exp(b^3_{jk}) \qquad \forall j \in U^3, k \in K^{3'} \tag{55}$$

$$\alpha^6_{ihjk} = \frac{\exp(t^1_{ihj} + b^6_{ihjk})}{T^0_{ihj} + \exp(t^1_{ihj} + b^6_{ihjk})} \qquad \forall (i,j,h) \in I \times H \times (E^3 \setminus E^{3'}), k \in K^{6'} \tag{56}$$

$$\alpha^7_{ihk} = \exp(b^7_{ihk} + \ln(d_i) - \ln(\delta)) \qquad \forall (i,h) \in I \times H, k \in K^{7'} \tag{57}$$

$\boldsymbol{\alpha}$ values for upper approximations

$$\alpha^1_{jk} = \frac{\beta^1_{j,k+1} - \beta^1_{j,k}}{a^1_j} \qquad \forall j \in U^1, k \in K^1 \tag{58}$$

$$\alpha^2_{jk} = \frac{\beta^2_{j,k+1} - \beta^2_{j,k}}{a^2_j} \qquad \forall j \in U^2, k \in K^2 \tag{59}$$

$$\alpha^3_{jk} = \frac{\beta^3_{j,k+1} - \beta^3_{j,k}}{a^3_j} \qquad \forall j \in U^3, k \in K^3 \tag{60}$$

$$\alpha^6_{ihjk} = \frac{\beta^6_{i,h,j,k+1} - \beta^6_{i,h,j,k}}{a^6_{ihj}} \qquad \forall (i,h,j) \in I \times H \times (E^3 \setminus E^{3'}), k \in K^{6'} \tag{61}$$

$$\alpha^7_{ihk} = \frac{\beta^7_{i,h,k+1} - \beta^7_{i,h,k}}{a^7_{ih}} \qquad \forall (i,h) \in I \times H, k \in K^7 \tag{62}$$

Notations

Indices and sets

I	Set of products i
H	Set of hosts h
E	Set of stages j
E^1	Set of batch stages j
E^2	Set of semicontinuous stages j
$E^{2'}$	Subset of semicontinuous stages j with permeate units
E^3	Set of chromatographic stages j
$E^{3'}$	Subset of gel filtration chromatographic stages j
K	Set of available units operating in-phase or out-of-phase
$K^{1'}$	Set of cutting points k for batch units or retentate/feed tank in semicontinuous or chromatographic stages: $K^{1'} = 1..NK1 + 1$
K^1	Set of linear functions for approximations for batch units or retentate/feed tank in semicontinuous or chromatographic stages: $K^1 = 1..NK1$
$K^{2'}$	Set of cutting points k for semicontinuous units with permeate tanks and chromatographic stages: $K^{2'} = 1..NK2 + 1$
K^2	Set of linear functions for approximations for semicontinuous units with permeate tanks and chromatographic stages: $K^2 = 1..NK2$
$K^{3'}$	Set of cutting points k for semicontinuous or chromatographic stages: $K^{3'} = 1..NK3 + 1$
K^3	Set of linear functions for approximations for semicontinuous or chromatographic stages: $K^3 = 1..NK3$
$K^{6'}$	Set of cutting points k to approximate time constraint of chromatographic stages: $K^{6'} = 1..NK6 + 1$
K^6	Set of linear functions to approximate time constraint of chromatographic stages: $K^6 = 1..NK6$
$K^{7'}$	Set of cutting points k to approximate planning horizon constraint: $K^{7'} = 1..NK7 + 1$
K^7	Set of linear functions to approximate planning horizon constraint: $K^7 = 1..NK7$

Variables

y_j^1	logarithmic volumetric capacity for tanks in batch stages and retentate or feed tanks for semicontinuous and chromatographic stages
y_j^2	logarithmic volumetric capacity for permeate or product tanks for semicontinuous and chromatographic stages
y_j^3	logarithmic size of the semicontinuous or chromatographic unit which can be, for example, a processing rate in the case of an homogenizer or an area in the case of a filter
y_{ih}^4	logarithmic final batch size, in mass units, of product i synthesized by host h
y_{ih}^5	logarithmic cycle time of product i synthesized by host h
x_j^1	number of units operating in-phase
x_j^2	number of units operating out-of-phase
y_{jk}^6	binary variables to account for a discrete number of units duplicated and operating in-phase
y_{jk}^7	binary variables to account for a discrete number of units duplicated and operating out-of-phase
z_{ih}^1	binary variable that is 1 if product i is synthesized by host h
z_j^2	binary variable that is 1 if stage j is part of the production path
r	Slack variable
v_j^1	auxiliary variable to replace cost function of y_j^1
v_j^2	auxiliary variable to replace cost function of y_j^2
v_j^3	auxiliary variable to replace cost function of y_j^3

Parameters

s^1_{ihj}	Constant size factor for batch stages or retentate/feed tank in semicontinuous or chromatographic stages for product i that was synthesized by host h and processed in stage j
s^2_{ihj}	Constant size factor for permeate/product tanks in semicontinuous or chromatographic stages for product i that was synthesized by host h and processed in stage j
s^3_{ihj}	Constant size factor for chromatographic columns for product i that was synthesized by host h and processed in stage j
t^0_{ihj}	Constant time factor for batch and chromatographic stages for product i that was synthesized by host h and processed in stage j
t^1_{ihj}	Constant time factor for semicontinuous and chromatographic stages for product i that was synthesized by host h and processed in stage j
c^1_j	cost coefficient for batch stage j of for retentate/feed tank of semicontinuos or chromatographic stage j
c^2_j	cost coefficient for permeate/product tank of semicontinuous of chromatographic stage j
c^3_j	cost coefficient for chromatographic column in stage j
γ^1_j	cost coefficient for batch stage j of for retentate/feed tank of semicontinuos or chromatographic stage j
γ^2_j	cost coefficient for permeate/product tank of semicontinuous of chromatographic stage j
γ^3_j	cost coefficient for chromatographic column in stage j
ρ	appropriate constant comparable to c_j parameters
d_i	overall amount of product i to be made within the time horizon δ
δ	time horizon