Supporting Information

Integrated Optimisation of Upstream and Downstream Processing in Biopharmaceutical Manufacturing under Uncertainty: A Chance Constrained Programming Approach

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1. Literature model
The literature MILP model\(^{19}\) for the optimal chromatography strategies of antibody purification processes is presented as follows.

The integer variables, \(CN_{si}\), \(CY_{Ns}\) and \(BN\), are expressed by binary variables:

\[
CN_{si} = \sum_{j=1}^{js} j \cdot W_{sij}, \ \forall s \in CS, i \quad (S. 1)
\]

\[
\sum_{j=1}^{js} W_{sij} = X_{si}, \ \forall s \in CS \quad (S. 2)
\]

\[
CY_{Ns} = \sum_{k=1}^{ks} k \cdot Y_{sk}, \ \forall s \in CS \quad (S. 3)
\]

\[
\sum_{k=1}^{ks} Y_{sk} = 1, \ \forall s \in CS \quad (S. 4)
\]

\[
BN = \sum_{n=1}^{q} 2^{n-1} \cdot Z_{n} \quad (S. 5)
\]

For each packed-bed chromatography step, only one resin can be used:

\[
\sum_{r \in R_s} U_{sr} = 1, \ \forall s \in CS \quad (S. 6)
\]

At most one resin of each resin type can be used:

\[
\sum_{s \in CS} \sum_{r \in R_s \cap R_t} U_{sr} \leq 1, \ \forall t \quad (S. 7)
\]

The initial product protein mass, \(M_0\), is the protein mass from the upstream bioreactors:

\[
M_0 = \text{titre} \cdot \alpha \cdot brv \quad (S. 8)
\]

The product protein mass remaining after step \(s\), \(M_s\) is related to the yield of the step:

\[
M_s = n \cdot cy_s \cdot M_{s-1}, \ \forall s \notin CS \quad (S. 9)
\]

\[
M_s = \sum_{r \in R_s} (cy_s \cdot \overline{UM}_{s-1,r}), \ \forall s \in CS \quad (S. 10)
\]

\[
\overline{UM}_{s-1,r} \leq \text{titre} \cdot \alpha \cdot brv \cdot U_{sr}, \ \forall s \in CS, r \in R_s \quad (S. 11)
\]

\[
\sum_{r \in R_s} \overline{UM}_{s-1,r} = M_{s-1}, \ \forall s \in CS \quad (S. 12)
\]

The annual product output, \(AP\), is amount of product produced per year by the facility:

\[
AP = \sum_{n=1}^{q} \sigma \cdot 2^{n-1} \cdot \overline{ZM}_{sn}, \ \forall s = bf \quad (S. 13)
\]

\[
\overline{ZM}_{sn} \leq \text{titre} \cdot \alpha \cdot brv \cdot Z_n, \ \forall s = bf, n = 1, ..., q \quad (S. 14)
\]

\[
\overline{ZM}_{sn} \leq M_s, \ \forall s = bf, n = 1, ..., q \quad (S. 15)
\]

\[
\overline{ZM}_{sn} \geq M_s - \text{titre} \cdot \alpha \cdot brv \cdot (1 - Z_n), \ \forall s = bf, n = 1, ..., q \quad (S. 16)
\]
The number of completed batches, $BN$, is limited by an upper bound:

$$BN \leq \text{maxbn} \quad (S.17)$$

The total column volume of chromatography step $s$, $TCV_s$, is the number of columns, $CN_{si}$, multiplied by the single column volume, $cv_{si}$:

$$TCV_s = \sum_i cv_{si} \cdot CN_{si}, \ \forall s \in CS \quad (S.18)$$

Only one column size is allowed at each chromatography step.

$$\sum_i X_{si} = 1, \ \forall s \in CS \quad (S.19)$$

$$CN_{si} \leq \text{maxcn}_{s} \cdot X_{si}, \ \forall s \in CS, i \quad (S.20)$$

The total amount of resin available is no less than the minimum required amount, $RV_s$:

$$\sum_{k=1}^{k_s} k \cdot \overline{V}_{sk} \geq RV_s, \ \forall s \in CS \quad (S.21)$$

$$\overline{V}_{sk} \leq \text{maxcn}_{s} \cdot \text{maxcv}_{s} \cdot Y_{sk}, \ \forall s \in CS, k = 1, \ldots, k_s \quad (S.22)$$

$$\sum_{k=1}^{k_s} \overline{V}_{sk} = TCV_s, \ \forall s \in CS \quad (S.23)$$

$$RV_s = \sum_{r \in R_s} \frac{\overline{UM}_{s-1 \cdot r} \cdot \overline{d} \cdot \overline{bc} \cdot \overline{r} \cdot \overline{\mu}}{\overline{r}} \quad \forall s \in CS \quad (S.24)$$

The number of cycles, $CYN_s$, at each chromatography step has an upper bound:

$$CYN_s \leq \text{maxyn}_{s}, \ \forall s \in CS \quad (S.25)$$

Volumetric flow rate, $VFR_s$, is determined by the velocity of flow and the diameter of the column:

$$VFR_s = \frac{1}{1000} \cdot \frac{1}{60} \cdot \sum_{r \in R_s} \sum_i \text{vel}_r \cdot \pi \cdot \left(\frac{dm_{si}}{2}\right)^2 \cdot \overline{U}_{X_{sri}}, \ \forall s \in CS \quad (S.26)$$

$$\sum_{r \in R_s} \overline{U}_{X_{sri}} = X_{si}, \ \forall s \in CS, i \quad (S.27)$$

$$\sum_i \overline{U}_{X_{sri}} = U_{sr}, \ \forall s \in CS, r \in R_s \quad (S.28)$$

The initial product volume entering downstream processes, $PV_0$, is the working volume of bioreactor:

$$PV_0 = \alpha \cdot brv \quad (S.29)$$
The product volume remaining after each step \( s \), \( PV_s \), and the required buffer material volume at each step \( s \), \( BV_s \), are given in Eq. (A30)-(S.43):

\[
PV_s = (fvr_s + 1) \cdot PV_0, \forall s = h
\]

\[
BV_s = fvr_s \cdot PV_0, \forall s = h
\]

\[
PV_s = \sum_{r \in R_{s} \cap FTR} ecv_r \cdot k \cdot \overline{UV}_{srk} + \sum_{r \in R_{s} \cap FTR} \overline{UV}_{s-1,r}, \forall s \in CS
\]

\[
BV_s = \sum_{r \in R_{s}} \sum_{k=1}^{k_{s}} bcv_r \cdot k \cdot \overline{UV}_{srk}, \forall s \in CS
\]

\[
\overline{UV}_{srk} \leq \max cn_s \cdot \max cv_s \cdot U_{sr}, \forall s \in CS, r \in R_s, k = 1, ..., k_s
\]

\[
\sum_{r \in R_s} \overline{UV}_{srk} = \overline{VV}_{sk}, \forall s \in CS, k = 1, ..., k_s
\]

\[
\overline{UV}_{s-1,r} \leq \max pv_{s-1} \cdot U_{sr}, \forall s \in CS, r \in R_s
\]

\[
\sum_{r \in R_s} \overline{UV}_{s-1,r} = PV_{s-1}, \forall s \in CS
\]

\[
PV_s = (nv r_s + 1) \cdot PV_{s-1}, \forall s = vi
\]

\[
BV_s = nvr_s \cdot BV_{s-1}, \forall s = vi
\]

\[
PV_s = (fvr_s + 1) \cdot PV_{s-1}, \forall s = vf
\]

\[
BV_s = fvr_s \cdot BV_{s-1}, \forall s = vf
\]

\[
PV_s = \frac{M_s}{fconc}, \forall s = ufdf
\]

\[
BV_s = dvr_s \cdot \frac{M_s}{fconc}, \forall s = ufdf
\]

The total buffer usage per batch, \( BBV \), is the summation of buffer usage, \( BV_s \), in all downstream steps:

\[
BBV = \sum_s BV_s
\]

The annual total buffer volume, \( ABV \), is related to the number of completed batches:

\[
ABV = \sum_{n=1}^{q} 2^n - 1 \cdot \overline{V}_n
\]

\[
\overline{V}_n \leq \max bbv \cdot Z_n, \forall n = 1, ..., q
\]

\[
\overline{V}_n \leq BBV, \forall n = 1, ..., q
\]

\[
\overline{V}_n \geq BBV - \max bbv \cdot (1 - Z_n), \forall n = 1, ..., q
\]

The total processing time at each chromatography step, \( T_s \), is comprised of processing time for both adding buffer (\( PLT_s \)) and loading product (\( BAT_s \)):

\[
T_s = PLT_s + BAT_s, \forall s \in CS
\]
The processing time for loading product, $PLT_s$, is related to the incoming product volume:

\[
\frac{1}{1000} \cdot \frac{1}{60} \sum_{r \in R_S} \sum_i \sum_{j=1}^{js} \text{vel}_r \cdot \pi \cdot \left(\frac{dm_{si}}{2}\right)^2 \cdot j \cdot \overline{UWT}_{srij} = PV_{s-1}, \; \forall \; s \in CS
\]  
(S.50)

\[
\overline{UWT}_{srij} \leq b_{rt} \cdot W_{sij}, \; \forall \; s \in CS, r \in R_s, i, j = 1, ..., js
\]  
(S.51)

\[
\overline{UWT}_{srij} \leq b_{rt} \cdot U_{sr}, \; \forall \; s \in CS, r \in R_s, i, j = 1, ..., js
\]  
(S.52)

\[
\sum_i \sum_{j=1}^{js} \sum_{r \in R_S} \overline{UWT}_{srij} = PLT_s, \; \forall \; s \in CS
\]  
(S.53)

The processing time for adding buffer, $BAT_s$, is related to the required buffer volume:

\[
BAT_s = \sum_{r \in R_s} \sum_i \sum_{k=1}^{ks} \frac{bcv_{r-cv_{sk}} k \overline{UXY}_{srik}}{\frac{1}{1000} \cdot \frac{1}{60} \cdot \text{vel}_r \cdot \pi \cdot \left(\frac{dm_{sk}}{2}\right)^2}, \; \forall \; s \in CS
\]  
(S.54)

\[
\sum_{r \in R_s} \sum_i \sum_{k=1}^{ks} \overline{UXY}_{srik} = Y_{sk}, \; \forall \; s \in CS, k = 1, ..., ks
\]  
(S.55)

\[
\sum_{k=1}^{ks} \overline{UXY}_{srik} = \overline{UX}_{sri}, \; \forall \; s \in CS, r \in R_s, i
\]  
(S.56)

The processing time per batch, $BT$, is the summation of processing time of all downstream steps:

\[
BT = \frac{\sum_{s} T_s}{60 \cdot sf \cdot sfn}
\]  
(S.57)

The annual DSP time, $AT$, is related to the number of completed batches:

\[
AT = \sum_{n=1}^{q} 2^{n-1} \cdot \overline{ZT}_{n}
\]  
(S.58)

\[
\overline{ZT}_{n} \leq (aot - st - b_{rt}) \cdot Z_n, \; \forall \; n = 1, ..., q
\]  
(S.59)

\[
\overline{ZT}_{n} \leq BT, \; \forall \; n = 1, ..., q
\]  
(S.60)

\[
\overline{ZT}_{n} \geq BT - (aot - st - b_{rt}) \cdot (1 - Z_n), \; \forall \; n = 1, ..., q
\]  
(S.61)

The annual DSP time, $AT$, cannot exceed the annual available time:

\[
AT \leq aot - st - b_{rt}
\]  
(S.62)

The labour cost, $LC$, involves the direct labour cost, $DLC$, supervisors cost, $SC$, quality control and quality assurance (QCQA) cost, $QC$, and management cost, $MC$:

\[
LC = DLC + SC + QC + MC
\]  
(S.63)

\[
DLC = 24 \cdot uon \cdot w \cdot b_{rt} \cdot BN + don \cdot w \cdot sf \cdot sfn \cdot AT
\]  
(S.64)

\[
SC = s\lambda \cdot DLC
\]  
(S.65)

\[
QC = q\lambda \cdot DLC
\]  
(S.66)

\[
MC = m\lambda \cdot DLC
\]  
(S.67)
The chemical reagents cost, \( CRC \), is assumed to include the cost for buffer, \( BC \), and bioreactor media, \( MEC \):

\[
CRC = BC + MEC \tag{S.68}
\]

\[
BC = bpc \cdot ABV \tag{S.69}
\]

\[
MEC = \theta \cdot mepc \cdot \alpha \cdot brv \cdot BN \tag{S.70}
\]

The key consumables cost, \( CC \), in this study is the resin cost:

\[
CC = \sum_{s \in CS} \sum_{r \in R_s} \sum_{q} \cdot \sum_{n=1}^{\text{of \_ \_ \_ \_ \_}} \cdot \Sigma_{k=1}^{p_{pc}} \cdot 2^{n-1} \cdot k \cdot Z\bar{U}Y\bar{V}_{srkn} \tag{S.71}
\]

\[
\bar{Z}\bar{U}Y\bar{V}_{srkn} \leq \text{maxtcvs} \cdot Z_n, \ \forall s \in CS, r \in R_s, k = 1, ..., k_s, n = 1, ..., q \tag{S.72}
\]

\[
\bar{Z}\bar{U}Y\bar{V}_{srkn} \leq \bar{U}Y\bar{V}_{srk}, \ \forall s \in CS, r \in R_s, k = 1, ..., k_s, n = 1, ..., q \tag{S.73}
\]

\[
\bar{Z}\bar{U}Y\bar{V}_{srkn} \geq \bar{U}Y\bar{V}_{sk} - \text{maxtcvs} \cdot (1 - Z_n), \ \forall s \in CS, r \in R_s, k = 1, ..., k_s, n = 1, ..., q \tag{S.74}
\]

The miscellaneous material cost, \( MIC \), is proportional to the total chemical reagents cost, \( CRC \), and consumables cost, \( CC \).

\[
MIC = m\iota \lambda \cdot (CRC + CC) \tag{S.75}
\]

The utilities cost, \( UC \), can be expressed as the summation of three terms:

\[
UC = a \cdot brn \cdot brv + b \cdot brv \cdot BN + c \cdot ABV \tag{S.76}
\]

The annualised capital cost, \( CAC \), is calculated by the fixed capital investment, \( FCI \), and the capital recovery factor:

\[
CAC = FCI \cdot \frac{r \cdot (1+r)^{el}}{(1+r)^{el-1}} \tag{S.77}
\]

\[
FCI = lang \cdot (1 + gef) \cdot (brn \cdot brc + \sum_{s \in CS} \sum_{i} cc_{si} \cdot CN_{si} + o\iota \lambda \cdot brc \cdot brn) \tag{S.78}
\]

Other indirect costs include the annual maintenance cost, \( MAC \), insurance cost, \( IC \), local tax costs, \( TC \), and general utilities cost, \( GUC \):

\[
MAC = m\alpha \lambda \cdot FCI \tag{S.79}
\]

\[
IC = i\alpha \lambda \cdot FCI \tag{S.80}
\]

\[
TC = t\alpha \lambda \cdot FCI \tag{S.81}
\]

\[
GUC = gu \cdot brn \cdot brv \tag{S.82}
\]

\[
OIC = MAC + IC + TC + GUC \tag{S.83}
\]
The annual total cost of goods is the summation of the above costs:

\[ COG = LC + CRC + CC + MIC + UC + CAC + OIC \] (S.84)

The objective is to minimise \( \frac{COG}{AP} \):

\[ OBJ = \frac{COG}{AP} \] (S.85)

**Nomenclature**

**Indices**
- \( bf \) bulk fill step
- \( h \) harvest step
- \( i \) column size
- \( j \) column number
- \( k \) cycle number
- \( n \) digit of the binary representation
- \( r \) resin
- \( s \) downstream step
- \( t \) resin type
- \( ufdf \) UF/DF step
- \( vf \) virus filtration step
- \( vi \) virus inactivation step

**Sets**
- \( BER \) set of resins in bind-elute mode
- \( CS \) set of chromatography steps, = capture, intermediate purification, polishing
- \( FTR \) set of resins in flow-through mode
- \( R_s \) set of resins suitable to chromatography step \( s \)
- \( R_t \) set of resins of the resin type \( t \)

**Parameters**
- \( a, b, c \) utilities cost coefficients
- \( aot \) annual operating time, day
- \( bcv_r \) buffer usage of resin \( r \), CV
- \( bpc \) buffer price, £/L
- \( brc \) bioreactor cost at given discrete volume for piecewise approximation, £
- \( brf \) scale-up factor of bioreactor cost
- \( brn \) number of bioreactors
- \( brt \) bioreaction time, day
- \( brv \) given discrete bioreactor volume for piecewise approximation, L
- \( cc_{si} \) column cost of size \( i \) at chromatography step \( s \), £
- \( c_f \) scale-up factor of column cost
- \( cv_{si} \) volume of column size \( i \) at chromatography step \( s \), L
- \( cy_{sr} \) product yield of resin \( r \) at chromatography step \( s \)
- \( dbc_r \) dynamic binding capacity of resin \( r \), g/L
- \( dm_{si} \) diameter of column size \( i \) at chromatography step \( s \), L
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>don</td>
<td>number of operators for downstream processing</td>
</tr>
<tr>
<td>dvr_s</td>
<td>diafiltration volume ratio of step s</td>
</tr>
<tr>
<td>ecv_r</td>
<td>elute volume of resin r, CV</td>
</tr>
<tr>
<td>el</td>
<td>equipment lifetime, year</td>
</tr>
<tr>
<td>fcon</td>
<td>final concentration of product, g/L</td>
</tr>
<tr>
<td>fvr_s</td>
<td>flush volume ratio of step s</td>
</tr>
<tr>
<td>gef</td>
<td>general equipment factor</td>
</tr>
<tr>
<td>gu</td>
<td>general utility unit cost, £/L</td>
</tr>
<tr>
<td>h_{si}</td>
<td>height of column size i at step s, cm</td>
</tr>
<tr>
<td>i\lambda</td>
<td>insurance cost ratio to the fixed capital investment</td>
</tr>
<tr>
<td>j_s</td>
<td>maximum number of columns at chromatography step s, maxcn_s</td>
</tr>
<tr>
<td>k_s</td>
<td>maximum number of cycles at chromatography step s, maxcyn_s</td>
</tr>
<tr>
<td>l_r</td>
<td>life time of resin r, cycle</td>
</tr>
<tr>
<td>lang</td>
<td>Lang factor</td>
</tr>
<tr>
<td>maxvv</td>
<td>maximum buffer volume per batch</td>
</tr>
<tr>
<td>maxbn</td>
<td>maximum number of batches</td>
</tr>
<tr>
<td>maxbrv</td>
<td>maximum bioreactor volume</td>
</tr>
<tr>
<td>maxcn_s</td>
<td>maximum number of columns at chromatography step s</td>
</tr>
<tr>
<td>maxcvs</td>
<td>maximum column volume at chromatography step s</td>
</tr>
<tr>
<td>maxcyns</td>
<td>maximum number of cycles at chromatography step s</td>
</tr>
<tr>
<td>maxpv_s</td>
<td>maximum product volume at step s</td>
</tr>
<tr>
<td>ma\lambda</td>
<td>maintenance cost ratio to the fixed capital investment</td>
</tr>
<tr>
<td>mepc</td>
<td>media price, £/L</td>
</tr>
<tr>
<td>mi\lambda</td>
<td>miscellaneous material cost ratio to chemical reagent and consumable costs</td>
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<tr>
<td>m\lambda</td>
<td>management cost ratio to direct labour cost</td>
</tr>
<tr>
<td>ncy_s</td>
<td>product yield of non-chromatography step s</td>
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<tr>
<td>nvr_s</td>
<td>neutralisation volume ratio of step s</td>
</tr>
<tr>
<td>oe\lambda</td>
<td>other equipment cost ratio to the bioreactor cost</td>
</tr>
<tr>
<td>of</td>
<td>overpacking factor of resin</td>
</tr>
<tr>
<td>q</td>
<td>maximum digit number in the binary representation of number of batches, $[\log_2 maxbn]$</td>
</tr>
<tr>
<td>q\lambda</td>
<td>QCQA cost ratio to direct labour cost</td>
</tr>
<tr>
<td>r</td>
<td>interest rate</td>
</tr>
<tr>
<td>rpc_r</td>
<td>resin price of resin r, £/L</td>
</tr>
<tr>
<td>refbrc</td>
<td>reference cost of a bioreactor, £</td>
</tr>
<tr>
<td>refbrv</td>
<td>reference volume of a bioreactor, L</td>
</tr>
<tr>
<td>refcc</td>
<td>reference cost of a chromatography column, £</td>
</tr>
<tr>
<td>refdm</td>
<td>reference diameter of a chromatography column, cm</td>
</tr>
<tr>
<td>sfd</td>
<td>duration per shift, hour</td>
</tr>
<tr>
<td>sfn</td>
<td>number of shifts per day</td>
</tr>
<tr>
<td>st</td>
<td>seed train bioreaction time, day</td>
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<tr>
<td>s\lambda</td>
<td>supervisors cost ratio to direct labour cost</td>
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<td>titre</td>
<td>upstream product titre, g/L</td>
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<tr>
<td>t\lambda</td>
<td>tax cost ratio to the fixed capital investment</td>
</tr>
<tr>
<td>uon</td>
<td>number of operators per bioreactor in upstream processing</td>
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<td>vel_r</td>
<td>linear velocity of flow for resin r, cm/h</td>
</tr>
<tr>
<td>w</td>
<td>wage of an operator, £/h</td>
</tr>
<tr>
<td>a</td>
<td>bioreactor working volume ratio</td>
</tr>
<tr>
<td>\theta</td>
<td>media overfill allowance</td>
</tr>
</tbody>
</table>
\( \mu \) chromatography resin utilisation factor
\( \sigma \) batch success rate

**Continuous Variables**

\( ABV \) annual buffer volume, L
\( AP \) annual product output, g
\( AT \) annual downstream operating time, day
\( BAT_s \) time for adding buffer per batch at chromatography step \( s \), min
\( BBV \) buffer volume added per batch, L
\( BC \) buffer cost, £
\( BRC \) bioreactor cost, £
\( BT \) downstream processing time per batch, day
\( BV_s \) buffer volume per batch in chromatography step \( s \), L
\( CAC \) capital cost, £
\( CC \) consumables cost, £
\( COG \) annual cost of goods, £
\( CRC \) chemical reagents cost, £
\( DLC \) direct labour cost, £
\( FCI \) fixed capital investment, £
\( GUC \) general utility cost, £
\( IC \) insurance cost, £
\( LC \) labour cost, £
\( M_0 \) initial product mass entering downstream processes per batch, g
\( M_s \) initial product mass per batch after step \( s \), g
\( MAC \) maintenance cost, £
\( MC \) management cost, £
\( MEC \) media cost, £
\( MIC \) miscellaneous material cost, £
\( OBJ \) objective
\( OIC \) other indirect costs, £
\( PLT_s \) time for loading product per batch at chromatography step \( s \), min
\( PV_0 \) initial product volume entering downstream processes per batch, L
\( PV_s \) product volume per batch after step \( s \), L
\( QC \) QCQA cost, £
\( RV_s \) resin volume required at chromatography step \( s \), L
\( SC \) supervisors cost, £
\( T_s \) processing time per batch of step \( s \), min
\( TC \) tax cost, £
\( TCV_s \) total column volume at chromatography step \( s \), L
\( UC \) utilities cost, £
\( VFR_s \) volumetric flow rate at chromatography step \( s \), L/min

**Binary Variables**

\( U_{sr} \) 1 if resin \( r \) is selected at chromatography step \( s \); 0 otherwise
\( W_{si,j} \) 1 if there are \( j \) columns of size \( i \) at chromatography step \( s \); 0 otherwise
\( X_{si} \) 1 if column size \( i \) is selected at chromatography step \( s \); 0 otherwise
\( Y_{sk} \) 1 if there are \( k \) cycles at chromatography step \( s \); 0 otherwise
\( Z_{n} \) 1 if the \( n \)th digit of the binary representation of variable \( BN \) is equal to 1; 0 otherwise
Integer Variables

\( BN \)  
number of completed batches

\( CN_{si} \)  
number of columns of size \( i \) at chromatography step \( s \)

\( CYN_{s} \)  
number of cycles at chromatography step \( s \)

Auxiliary Variables

\( \bar{UM}_{s-1,r} \)  
\( \equiv U_{sr} \cdot M_{s-1} \)

\( \bar{UV}_{s-1,r} \)  
\( \equiv U_{sr} \cdot PV_{s-1} \)

\( \bar{UW}_{sti}^{rsij} \)  
\( \equiv U_{sr} \cdot W_{sij} \cdot PLT_{s} \)

\( \bar{UX}_{sri} \)  
\( \equiv U_{sr} \cdot X_{si} \)

\( \bar{UXY}_{sri}^{rsjk} \)  
\( \equiv U_{sr} \cdot X_{si} \cdot Y_{sk} \)

\( \bar{UYY}_{sri}^{rsjk} \)  
\( \equiv U_{sr} \cdot Y_{sk} \cdot TCV_{s} \)

\( \bar{YW}_{s} \)  
\( \equiv Y_{sk} \cdot TCV_{s} \)

\( \bar{ZM}_{sn} \)  
\( \equiv Z_{n} \cdot M_{s} \)

\( \bar{ZT}_{sn} \)  
\( \equiv Z_{n} \cdot BT \)

\( \bar{ZV}_{sn} \)  
\( \equiv Z_{n} \cdot BBV \)

\( \bar{ZUY}_{srkn} \)  
\( \equiv Z_{n} \cdot U_{sr} \cdot Y_{sk} \cdot TCV_{s} \)

2. Case study data

More data of the case study are presented in Tables S1 and S2.

<table>
<thead>
<tr>
<th>Unit operation parameter</th>
<th>Value</th>
<th>Unit operation parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cell culture</strong></td>
<td></td>
<td><strong>Cell culture</strong></td>
<td></td>
</tr>
<tr>
<td>bioreaction time (days)</td>
<td>15</td>
<td>processing time (h)</td>
<td>1.5</td>
</tr>
<tr>
<td>seed train bioreaction time (days)</td>
<td>29</td>
<td>yield (%)</td>
<td>95</td>
</tr>
<tr>
<td>bioreactor working volume ratio (%)</td>
<td>75</td>
<td>flush volume ratio</td>
<td>0.3</td>
</tr>
<tr>
<td>media overfill factor</td>
<td>1.2</td>
<td>processing time (h)</td>
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</tr>
<tr>
<td>media price (£/L)</td>
<td>32</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Virus filtration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yield (%)</td>
<td>95</td>
<td>processing time (h)</td>
<td>4</td>
</tr>
<tr>
<td><strong>Harvest</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yield (%)</td>
<td>95</td>
<td>processing time (h)</td>
<td>4</td>
</tr>
<tr>
<td>flush volume ratio</td>
<td>0.1</td>
<td>final concentration (g/L)</td>
<td>75</td>
</tr>
<tr>
<td>processing time (h)</td>
<td>4</td>
<td>diafiltration volume</td>
<td>7</td>
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<tr>
<td><strong>Ultra/Diafiltration</strong></td>
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<td></td>
</tr>
<tr>
<td><strong>Virus inactivation</strong></td>
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<td></td>
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</tr>
<tr>
<td>yield (%)</td>
<td>90</td>
<td>filling time (h)</td>
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</tr>
<tr>
<td>neutralisation volume ratio</td>
<td>1.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bulk fill</strong></td>
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</table>
Table S2. More data for cost and time

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Value</th>
<th>Parameters</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \alpha_t ) (day)</td>
<td>340</td>
<td>( a ) (£/L)</td>
<td>14.145</td>
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<tr>
<td>( \delta_t ) (day)</td>
<td>15</td>
<td>( b ) (£/L)</td>
<td>4.234</td>
</tr>
<tr>
<td>( u_{on} ) (day)</td>
<td>3</td>
<td>( c ) (£/L)</td>
<td>0.071</td>
</tr>
<tr>
<td>( sf_d ) (hours/shift)</td>
<td>8</td>
<td>( \sigma )</td>
<td>90%</td>
</tr>
<tr>
<td>( sf_n ) (shift/day)</td>
<td>1</td>
<td>( q )</td>
<td>1</td>
</tr>
<tr>
<td>( w ) (£/h)</td>
<td>20</td>
<td>( m )</td>
<td>1</td>
</tr>
<tr>
<td>( b_{pc} ) (£/L)</td>
<td>1</td>
<td>( m_i )</td>
<td>0.1</td>
</tr>
<tr>
<td>( \sigma )</td>
<td>90%</td>
<td>( o_{e} )</td>
<td>0.8</td>
</tr>
<tr>
<td>( gef )</td>
<td>0.7</td>
<td>( m_{a} )</td>
<td>0.05</td>
</tr>
<tr>
<td>( gu ) (£/L)</td>
<td>90</td>
<td>( i )</td>
<td>0.005</td>
</tr>
<tr>
<td>( lang )</td>
<td>6</td>
<td>( t )</td>
<td>0.01</td>
</tr>
</tbody>
</table>