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Multi-objective optimisation for biopharmaceutical manufacturing under uncertainty

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ABSTRACT

This work addresses the multi-objective optimisation of manufacturing strategies of monoclonal antibodies under uncertainty. The chromatography sequencing and column sizing strategies, including resin at each chromatography step, number of columns, column diameters and bed heights, and number of cycles per batch, are optimised. The objective functions simultaneously minimise the cost of goods per gram and maximise the impurity reduction ability of the purification process. Three parameters are treated as uncertainties, including bioreactor titre, and chromatography yield and capability to remove impurities. Using chance constraint programming techniques, a multi-objective mixed integer optimisation model is proposed. Adapting both ε-constraint method and Dinkelbach's algorithm, an iterative solution approach is developed for Pareto-optimal solutions. The proposed model and approach are applied to an industrially-relevant example, demonstrating the benefits of the proposed model through Monte Carlo simulation. The sensitivity analysis of the confidence levels used in the chance constraints of the proposed model is also conducted.

1. Introduction

The market of biopharmaceutical products is currently in a fast-development stage, in which the sales of monoclonal antibodies (mAbs) products, important biopharmaceutical drugs for the treatment of cancer, autoimmune diseases, cardiovascular disease, etc., have grown rapidly. There were approximately $90 billion global sales in 2015, representing about 58% of the sales of all biopharmaceuticals. It is expected that the worldwide sales will increase to $110 billion by 2018 and $150 billion by 2021 (Levine and Cooney, 2017). In the manufacturing processes of the mAb products, chromatography operations in the downstream processing (DSP) are critical steps, which not only represent a large proportion of the total manufacturing cost, but also play an important role in the determination of the purity of final products. Thus, it is critical to identify the chromatography purification process in the biopharmaceutical manufacturing processes to produce cost-effective and reliable high-purity biopharmaceutical drugs.

Optimisation-based approaches exist in the literature for the optimal decision-making on downstream purification processes. The optimal synthesis of protein purification processes was addressed by developing mixed integer programming models and solution approaches (Vassquez-Alvarez et al., 2001; Simeonidis et al., 2005; Natali et al., 2009; Polykarpou et al., 2011). A metaheuristic optimisation approach with genetic algorithms was proposed and applied to the production of mAbs to optimise purification sequences and chromatography column sizing strategies (Simaria et al., 2012). Mixed integer optimisation models were also proposed to determine the optimal development of bioprocesses, using a hybrid simulation-optimisation decomposition algorithm for solution (Brunet et al., 2012). Mixed integer programming techniques were applied for the optimal chromatography column sizing decisions in mAb manufacturing with different facility configurations, to minimise the cost of goods per gram (COG/g) (Liu et al., 2013a,b). The same authors further extended these models to integrate both chromatography sequencing and column sizing decisions using mixed integer linear fractional programming (MILFP), where Dinkelbach's algorithm was adapted for solution approach (Liu et al., 2014, 2015). Integrated decision tools combining bioprocess economics and optimisation were developed for the most cost-effective process flowsheets in allogeneic cell therapy manufacturing (Simaria et al., 2014; Hassan et al., 2015). Recently, another approach for the optimisation of biopharmaceutical downstream processes was developed by integrating detailed mechanistic models and artificial neural networks to maximise the

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Nomenclature

Indices

r	resin
s	downstream step

Sets

CS	set of chromatography steps including capture, intermediate purification, polishing
R_s	set of resins suitable to chromatography step s

Parameters

A_s^l	confidence level in chance constraint for LRV at chromatography step s
A^t	confidence level in chance constraint for titre
A_s^y	confidence level in chance constraint for yield at chromatography step s
brv	bioreactor volume, L
cy_{sr}	yield of resin r at chromatography step s
cyd_s^l	lower bound of triangular distribution of yield deviation at chromatography step s
cyd_s^p	peak of triangular distribution of yield deviation at chromatography step s
cyd_s^u	upper bound of triangular distribution of yield deviation at chromatography step s
dem	annual demand, g
f	parameter in Dinkelbach's algorithm representing faction from previous iteration
lrv_{sr}	LRV of resin r at chromatography step s
$lrvd_s^l$	lower bound of triangular distribution of LRV deviation at chromatography step s
$lrvd_s^p$	peak of triangular distribution of LRV deviation at chromatography step s
$lrvd_s^u$	upper bound of triangular distribution of LRV deviation at chromatography step s
$maxbn$	maximum number of batches
ncy_s	yield at non-chromatography step s
$titre$	upstream bioreactor titre, g/L
$titre^l$	lower limit of triangular distribution of upstream bioreactor titre, g/L
$titre^p$	peak of triangular distribution of upstream bioreactor titre, g/L
$titre^u$	upper bound of triangular distribution of upstream bioreactor titre, g/L
$TLRV^{min}$	minimum required total LRV of the process
$TLRV^U$	upper bound of total LRV of the process
α	bioreactor working volume ratio
δ	parameter in Dinkelbach's algorithm representing tolerance of objective function
$\Delta TLRV$	incremental step of total LRV of the process
σ	batch success rate
Φ	triangular cumulative distribution function of uncertain titre
$\bar{\Phi}_s$	triangular cumulative distribution function of uncertain resin yield deviation
$\tilde{\Phi}_s$	triangular cumulative distribution function of uncertain resin LRV deviation

Continuous Variables

AP	annual product output, g
COG	annual cost of goods, £
LRV_s	LRV at chromatography step s
M_0	initial product mass entering downstream processes per batch, g
M_s	product mass per batch after step s, g
OBJ_1	objective 1: COG/g
OBJ_2	objective 2: total LRV

Binary Variables

U_{sr}	1 if resin r is selected at chromatography step s; 0 otherwise

Auxiliary Variables

$\overline{UM}_{s-1,r}$	$\equiv U_{sr} \cdot M_{s-1}$

yield of a process with three different chromatographic columns (Pirrung et al., 2017).

In addition, dealing with uncertainty is also an important issue investigated in the literature on the optimisation of biopharmaceutical manufacturing process, which is sensitive to uncertain process parameters. The cost-effective equipment sizing strategies of a real purification process were addressed and a combinatorial closed-loop optimisation problem was formulated and solved by evolutionary algorithm, considering uncertain titre (Allmendinger et al., 2012, 2014a). An optimisation framework was developed to address the integrated optimisation of both upstream processing (USP) and DSP of the mAb manufacturing, including bioreactor sizing and chromatography sequencing and column sizing strategies, under uncertainties in titre and chromatography yield. A chance constrained programming (CCP) based mixed integer linear programming (MILP) model was developed to tackle the uncertainties there (Liu et al., 2016). A Markov decision model was developed to identify the optimal condition-based bioreactor harvesting policies, and the IgG_1 antibody production was investigated as a case study (Martagan et al., 2016). Ensemble modelling approach was used to account for uncertainties in bioprocess optimisation involving maximisation of the lower confidence bound of the desired bioprocess objective, using a mean-standard deviation utility function, and was applied to a mAb batch production problem (Liu and Gunawan, 2017). An optimisation framework, including a Markov decision model and state space structural analysis, was developed to deal with the trade-offs between yield and purity, starting material uncertainties, purification capability limitations, and interlinked decisions involving multiple purification steps for engineered proteins (Martagan et al., 2018).

All above works considered only single objective for optimisation, while in the real practice, there is more than one criterion to measure the performance of manufacturing processes, which need to be taken into account simultaneously when optimising the relevant strategies, in order to achieve a balance among them. An optimisation framework with an evolutionary multi-objective optimisation algorithm was developed to consider multiple objectives, including COG/g, robustness in COG/g, and impurity removal capabilities, in the optimisation of mAb manufacturing process (Allmendinger et al., 2014b) Another decision-making framework on rapid resin selection in biopharmaceutical purification process development considered both yield of purification process and purity of the target protein as objective functions, which were optimised by a mathematical programming model (Liu et al., 2017). Recently, a deterministic multi-objective optimisation model of a biopharmaceutical manufacturing process was developed to optimise both the cost and impurity removal capabilities of the purification process (Liu and Papageorgiou, 2018).

In this work, the model in Liu et al. (2014) is extended to address the multi-objective optimisation of bio-

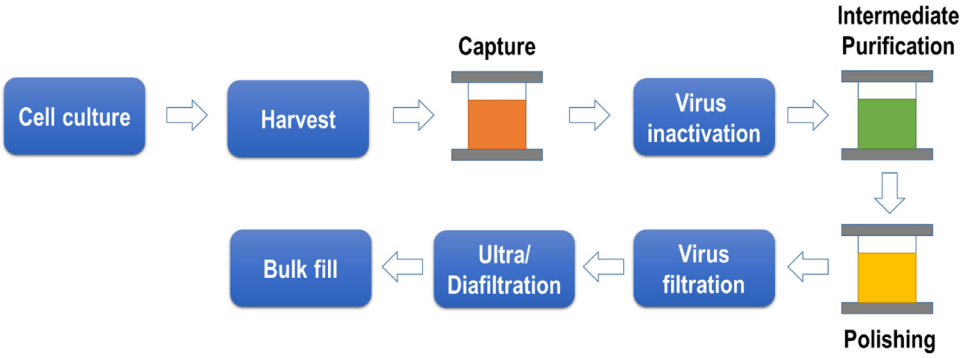

Fig. 1. A typical mAb manufacturing process.

pharmaceutical manufacturing processes under uncertainty. Both chromatography sequencing and column sizing strategies of a mAb purification process are determined in order to achieve optimal COG/g and impurity removal capability at the DSP. Uncertainties in titre, chromatography resin yield and impurity reduction ability are taken into account, which have a significant impact on the economic and production efficiency of the process, respectively. A CCP-based multi-objective mixed integer optimisation model is proposed to handle the uncertainties, and efficient solution approaches are developed for Pareto-optimal solutions. To the best of our knowledge, it is the first attempt in the literature to develop mathematical programming-based models to solve multi-objective optimisation problems of biopharmaceutical manufacturing under uncertainty.

The remaining of this paper is organised as follows: Section 2 describes the multi-objective optimisation problem. The mathematical formulation of the proposed optimisation model is given in Section 3, followed by the proposed solution approach in Section 4. Section 5 presents an industrially-relevant example, and the computational results of optimisation and simulation are shown and discussed in Section 6. Finally, the concluding remarks are drawn in Section 7.

2. Problem statement

In this work, a multi-objective optimisation problem of the mAb manufacturing strategies, including the chromatography sequencing and column sizing strategies in the DSP, under uncertainty are addressed, to optimise both COG/g and impurity removal capability of a mAb purification process illustrated in Fig. 1. In this process, after mammalian cells cultured in bioreactors at the USP, the mAb is recovered, purified and cleared from potential viruses and impurities in the DSP with three packed-bed chromatography steps for capture, intermediate purification and polishing, respectively.

In each chromatography step, the resin is determined among a number of suitable candidates, which are categorised in to different types. It is assumed that at most one resin is allowed to be selected from the candidates in each type into the sequence to utilities the orthogonal separation mechanisms. Besides the chromatography sequencing decisions for resin selection, chromatography column sizing strategies are also to be determined, including the bed heights, diameters, number of chromatography columns, as well as the number of running cycles per batch. The optimal decisions are chosen from a set of given discrete candidate values.

Similar to the previous work (Liu et al., 2013a,b, 2014, 2015), the COG/g, which is equal to the annual total cost of goods (COG) divided by the annual total output, is aimed to be minimised in this work. In addition, the impurity removal capability of the purification process is maximised as another objective function. Therefore, a bi-objective optimisation problem is considered in this work. To model the impurity removal capability, the host cell proteins (HCPs), produced or encoded by the organisms and unrelated to the intended mAb product, are investigated as the critical impurity in this work, and must be removed during DSP (Levy et al., 2014), due to their antigenic effects in patients. Each candidate resin's logarithmic removal value (LRV) of HCPs is given, a measure of the resin's HCPs removal capability defined as the logarithm of the ratio of concentrations of HCPs in the outflow and inflow of the resin. The total LRV of the process is the summation of LRVs of all resins selected in the process, and therefore affected by the chromatography sequencing strategies.

The key parameters in this problem, bioreactor titre and the chromatography yield and LRV of each resin, are associated with uncertainty, due to the fluctuations in USP and sensitivity of operating conditions. In this work, the above mentioned three uncertain parameters are assumed to follow triangular probability distributions (Stonier et al., 2013; Allmendinger et al., 2012, 2014a,b). It is also assumed that the realised values of each uncertain parameter remain the same in different batches (Liu et al., 2016).

The multi-objective optimisation problem addressed in this work can be described as follows:

Given are:

- manufacturing process of a mAb product;
- upstream bioreactor titre;
- candidate chromatography resins at each step, and their key characteristics, e.g., yield, linear velocity, buffer usage, dynamic binding capacity, and LRV of HCPs;
- key characteristics of non-chromatography steps, e.g., yield, time and buffer usage;
- relevant cost data, e.g., reference equipment costs, labour wage, resin, buffer and media prices;
- candidate column diameters and heights, numbers of columns and cycles;
- probability distributions of titre, chromatography yields and LRVs of HCPs;

To determine:

- chromatography sequencing strategies, i.e., resin at each chromatography step;
- chromatography column sizing strategies, i.e., column diameter and bed height, number of columns, and number of cycles per batch at each chromatography step;
- product mass and volume, and buffer usage volume;
- number of total completed batches;
- annual total processing time;

So as to:
minimise the COG/g and maximise the total LRV of the whole mAb purification process.

3. Mathematical formulation

In this section, a CCP-based multi-objective optimisation model for the optimal chromatography sequencing and sizing decisions is presented, to deal with uncertainties in titre and chromatography resin yields and LRVs of HCPs, based on the literature MILFP model for DSP purification process optimisation (Liu et al., 2014), which is given in the Supplementary Material. There are a large number of constraints and variables for the modelling of the highly complex process, including the product masses and volumes, buffer volumes and processing times in downstream operations, the calculation of relevant cost terms, and the linearisation the nonlinear constraints in the proposed optimisation model. Only the newly developed constraints in this work are presented in this section.

The uncertain upstream titre, chromatography resin yields and LRVs of HCPs are tackled using the classic CCP approach, in which a risk tolerance is determined by the decision maker as a permissible probability of violation in the constraints involving uncertain parameters (Charnes and Cooper, 1959). The developed chance constraints are transformed into their deterministic equivalent formulations using the expression of the inverse cumulative distribution function. The chance constraints for three parameter sets in the CCP approach are presented next in this section.

3.1. Chance constraints for uncertain titre

In the deterministic model, the initial protein mass from the upstream processes in each batch, M_0, is determined by the bioreactor titre, *titre*, and the working volume of bioreactor:

$$M_0 = titre \cdot \alpha \cdot brv \tag{1}$$

where α is the working volume ratio of the bioreactor, and *brv* is the volume of the single bioreactor, estimated by a rule-based method (Simaria et al., 2012; Liu et al., 2013a,b, 2016), as follows:

$$brv = \frac{dem}{\alpha \cdot titre \cdot maxbn \cdot \sigma \cdot \prod_{s\in CS} \min_{r\in R_s} cy_{sr} \cdot \prod_{s\notin CS} ncy_s} \tag{2}$$

where *dem* is the target demand; *maxbn* is the maximum batches allowed, determined by the number of bioreactors utilised; σ is batch success rate; and cy_{sr} and ncy_s are the yields at chromatography and non-chromatography steps, respectively.

When the parameter, *titre*, becomes uncertain, to develop a chance constraint to model uncertainty, Eq. (1) is firstly converted into an inequality, as shown in Eq. (3) in which M_0 is upper-bounded as it is maximised to achieve the minimum COG/g:

$$M_0 \le titre \cdot \alpha \cdot brv \tag{3}$$

The corresponding chance constraint is formulated by enforcing the probability of the inequality above a certain limit, as follows:

$$\Pr\left(M_0 \le titre \cdot \alpha \cdot brv\right) \ge A^t \tag{4}$$

where A^t is a minimum prespecified probability that Eq. (3) will hold true, as confidence level taking a value between 50% and 100%.

The above Eq. (4) can be written using the probability of the uncertain titre:

$$1 - \Pr\left(titre \le \frac{M_0}{\alpha \cdot brv}\right) \ge A^t \tag{5}$$

Here, the upstream titre is assumed to follow a triangular probability distribution, $\mathrm{Tr}(titre^l, titre^p, titre^u)$, where $titre^l$, $titre^p$ and $titre^u$ are lower bound, peak and upper bound, respectively. Its cumulative distribution function is denoted as $\Phi(titre)$. Thus, Eq. (5) can be rewritten as Eq. (6):

$$\Phi\left(\frac{M_0}{\alpha \cdot brv}\right) \le 1 - A^t \tag{6}$$

Using the inverse cumulative distribution function expression, the deterministic equivalent formulation of Eq. (3) is as follows:

$$M_0 \le \Phi^{-1}\left(1 - A^t\right) \cdot \alpha \cdot brv \tag{7}$$

For an isosceles triangular distribution where $titre^u - titre^p = titre^p - titre^l = \Delta titre$, $\Phi^{-1}(1 - A^t) = titre^l + \sqrt{2(1 - A^t)} \cdot \Delta titre$, if $A^t > 50\%$. The peak can also be used to estimate the bioreactor volume in Eq. (2).

3.2. Chance constraints for uncertain yields

The yield at a chromatography step links the product mass amount in the inflow and outflow of the step, determined by the selected resin's yield:

$$M_s = \sum_{r\in R_s} cy_{sr} \cdot \overline{UM}_{s-1,r}, \quad \forall s \in CS \tag{8}$$

where $\overline{UM}_{s-1,r}$ is an auxiliary variable to represent $U_{sr} \cdot M_{s-1}$, in which U_{sr} is a binary variable to indicate whether resin r is selected at chromatography step s, and M_s is the mAb mass of each batch after step s.

To model the uncertainty of resin yield, we introduce an uncertain parameter, cyd_s, to denote the deviation of the selected resin's yield from its standard value, cy_{sr}, at chromatography step s. Thus, we can convert the constraint involving the uncertainty of resin yields into an inequality as follows:

$$M_s \le \sum_{r\in R_s} cy_{sr} \cdot \overline{UM}_{s-1,r} \cdot cyd_s, \quad \forall s \in CS \tag{9}$$

Similarly, given a confidence level of Eq. (9) being true for each chromatography step s, A_s^y, its corresponding chance constraint can be formulated as:

$$\Pr\left(M_s \le \sum_{r\in R_s} cy_{sr} \cdot \overline{UM}_{s-1,r} \cdot cyd_s\right) \ge A_s^y, \quad \forall s \in CS \tag{10}$$

Here, the yield deviation, cyd_s, is an uncertain parameter following a triangular distribution, $\mathrm{Tr}(cyd_s^l, cyd_s^p, cyd_s^u)$. The peak cyd_s^p is 100%, while cyd_s^l and cyd_s^u are lower and upper bounds of the yield deviation at chromatography step s. The cumulative distribution function is denoted as $\bar{\Phi}_s(cyd_s)$. Thus, similar to the discussion to titre in Section 3.1, Eq. (10) can be reformulated as below:

$$M_s \le \bar{\Phi}_s^{-1}\left(1 - A_s^y\right) \cdot \sum_{r\in R_s} cy_{sr} \cdot \overline{UM}_{s-1,r}, \quad \forall s \in CS \tag{11}$$

where $\bar{\Phi}_s^{-1}(1 - A_s^y) = cyd_s^l + \sqrt{2(1 - A^t)} \cdot \Delta cyd_s$, if $cyd_s^u - cyd_s^p = cyd_s^p - cyd_s^l = \Delta cyd_s$ and $A_s^y > 50\%$.

3.3. Chance constraints for uncertain LRVs

To ensure the purity of the mAb product meets the target level after the purification process, HCPs, one of the critical impurities, must be removed during the process. The capability to remove HCPs of each resin is measured in terms of LRV, lrv_{sr}. Thus, the LRV at each chromatography step is determined by the selected resin:

$$LRV_s = \sum_{r\in R_s} lrv_{sr} \cdot U_{sr}, \quad \forall s \in CS \tag{12}$$

To generate a chance constraint for uncertain LRV, Eq. (12) is converted into an inequality, with the introduction of an uncertain parameter, $lrvd_s$, to represent the deviation of the selected resin's LRV from its standard value at chromatography step s, lrv_{sr}:

$$LRV_s \le \sum_{r\in R_s} lrv_{sr} \cdot U_{sr} \cdot lrvd_s, \quad \forall s \in CS \tag{13}$$

where LRV_s is restricted by an upper bound as it is aimed to be maximised at each step.

Similarly, the corresponding chance constraint of Eq. (13) with a given confidence level of its being valid, A_s^l, is as follows:

$$\Pr\left(LRV_s \le \sum_{r\in R_s} lrv_{sr}\cdot U_{sr}\cdot lrvd_s\right) \ge A_s^l,\ \ \forall s\in CS \tag{14}$$

The uncertain LRV deviation, $lrvd_s$, also follows a triangular distribution, $\mathrm{Tr}(lrvd_s^l, lrvd_s^p, lrvd_s^u)$, in which the peak, $lrvd_s^p$, is also 100%, and $lrvd_s^l$ and $lrvd_s^u$ are the corresponding lower and upper bounds. Given its cumulative distribution, $\tilde{\Phi}_s(lrvd_s)$, we have the following deterministic equivalent formulation of Eq. (13):

$$LRV_s \le \tilde{\Phi}_s^{-1}\left(1-A_s^l\right)\cdot\sum_{r\in R_s} lrv_{sr}\cdot U_{sr},\ \ \forall s\in CS \tag{15}$$

Here, under an isosceles triangular distribution where $lrvd_s^u - lrvd_s^p = lrvd_s^p - lrvd_s^l = \Delta lrvd_s$, we have $\tilde{\Phi}_s^{-1}(1-A_s^l) = lrvd_s^l + \sqrt{2(1-A_s^l)}\cdot\Delta lrvd_s$ when $A_s^l > 50\%$.

3.4. Objective functions

This problem includes two objective functions to simultaneously consider both cost and impurity reduction ability of the purification process. The first objective, COG/g, i.e., the ratio of the total COG, *COG*, to the annual production, *AP*, is minimised:

$$\text{Min } OBJ_1 = \frac{COG}{AP} \tag{16}$$

The second objective considers the maximisation of total impurity removal capability, which is represented by total LRV of the process, defined as the summation of the LRVs at all three chromatography steps:

$$\text{Max } OBJ_2 = \sum_{s\in CS} LRV_s \tag{17}$$

Overall, the optimisation problem under uncertainty is formulated as a CCP-based multi-objective optimisation model (denoted as MO–CCP) with chance constraints, Eqs. (7), (11), (15), as well as other constraints, Eqs. (S.1)-(S.7), (S.9), (S.11)-(S.84) provided in the Supplementary Material, and Eqs. (16) and (17) as the objective functions. When no uncertainty is considered, the deterministic optimisation model (denoted as MO-DET) includes Eqs. (12), (S.1)-(S.84) in the Supplementary Material as constraints, and Eqs. (16) and (17) as the objective functions, which will be compared to the proposed MO–CCP model later in this work.

4. Solution approach

To solve the proposed multi-objective optimisation model in the above section, we adapt the classic ε-constraint method (Haimes et al., 1971; Chankong and Haimes, 1983), where only one objective is optimised and all other objectives are converted into constraints by setting an upper or lower bound to each of them, to achieve the minimum-cost solution under total LRV requirement. The obtained solutions are proven to satisfy the Pareto optimality (Miettinen, 1999).

In the proposed multi-objective optimisation problem, between the two objectives, the COG/g is kept as the objective function, while the total LRV of HCPs is transformed as a constraint limited by a lower bound. Thus, the multi-objective model MO-CCP is reformulated as a single-objective optimisation model, SO–CCP, as follows:

$$\begin{aligned}&\text{Min } \tfrac{COG}{AP}\\ &\text{s.t. } \sum_{s\in CS} LRV_s \ge TLRV^{min}\\ &\quad \text{Eqs. (7), (11), (15), (S.1)−(S.7), (S.9), (S.11)−(S.84)}\end{aligned}$$

where $TLRV^{min}$ refers to the minimum required total LRV to ensure that the purity of final products is higher than the given target purity level. By changing the value of $TLRV^{min}$, a set of Pareto-optimal solutions can be achieved. The above SO–CCP model solved in each iteration of ε-constraint method is an MILFP model. Similar to the work of Liu et al. (2014, 2015, 2018), the Dinkelbach's algorithm (Dinkelbach, 1967) is applied to the MILFP model by iteratively solving a number of MILP models, MILP-CCP, defined as follows:

$$\begin{aligned}&\text{Min } COG - f\cdot AP\\ &\text{s.t. } \sum_{s\in CS} LRV_s \ge TLRV^{min}\\ &\quad \text{Eqs. (7), (11), (15), (S.1)−(S.7), (S.9), (S.11)−(S.84)}\end{aligned}$$

where f is a parameter whose value is updated by iterations.

Overall, the proposed iterative solution approach integrating both ε-constraint method and Dinkelbach's algorithm is illustrated in Fig. 2. The proposed iterative solution procedure consists of solving a number of CCP-based MILP models iteratively, resulting in a set of Pareto-optimal solutions of the developed multi-objective optimisation model under uncertainty, MO–CCP. Note that the similar procedure is also applicable to the deterministic multi-objective optimisation problem, MO-DET, by solving a collection of deterministic MILP models.

5. Case study

In this section, an industrially-relevant example, based on a mAb purification process in a biopharmaceutical company, is introduced to examine the applicability of the proposed models and approaches. There are 11 candidate commercial resins in two modes, binding-elution (BE) and flow-through (FT) and the following five types:

- affinity chromatography (AFF);
- cation-exchange chromatography (CEX
- anion-exchange chromatography (AEX);
- mixed-mode chromatography (MM);
- hydrophobic interaction chromatography (HIC).

The characteristics of these resin candidates are shown in Table 1, where the standard values of yield and LRV of each resin are shown, and their actual values during production may vary from those.

As to the chromatography column sizing decisions, 11 discrete potential bed heights and 10 discrete potential diameters are available for selection, as shown in Table 2. There also could be up to 4 parallel columns utilised at each chromatography step and each batch could run in at most 10 cycles.

Here, multiple USP trains could be used to feed one DSP train. According to the previous work (Liu et al., 2013a,b, 2014, 2015, 2016, 2017), single bioreactor has higher cost efficiency than other cases. Therefore, only one bioreactor is considered in this case study, while multiple bioreactors can be easily accommodated into the proposed models. Considering a target demand of 500 kg, the volume of the single bioreactor can be calculated using Eq. (2), which is 25,017 L. More data in the case study are given in the Supplementary Material (Tables S1-S3). The three uncertain parameters considered in this work all follow isosceles triangular probability distributions, as described in Table 3. It is assumed that different chromatography steps use the same distribution function considering uncertain yield and LRV deviation.

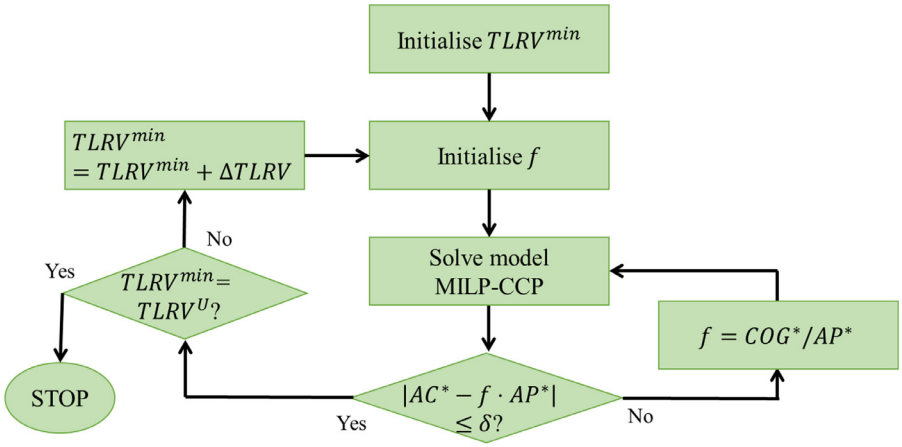

Fig. 2. The proposed iterative solution approach of the proposed MO–CCP model.

Table 1
Characteristics of resin candidates.

Resin	Type	Mode	Binding capacity (g/L)	Eluate volume (CV)	Buffer volume (CV)	Linear velocity (cm/h)	Matrix lifetime (cycle)	Matrix price (£/L)	Standard yield			Standard LRV of HCPs		
									Cap.	Int.	Pol.	Cap.	Int.	Pol.
R1	AFF	BE	50	2.3	37	150	100	9200	91%	95%	-	3	1.5	-
R2	AFF	BE	30	2.3	37	300	100	6400	91%	95%	-	3	1.5	-
R3	AFF	BE	50	2.3	37	800	100	9900	91%	95%	-	3	1.5	-
R4	AFF	BE	30	2.3	37	1000	100	9000	91%	95%	-	3	1.5	-
R5	CEX	BE	120	1.4	26	500	100	2500	86%	-	-	2	-	-
R6	CEX	BE	40	1.4	26	300	100	400	86%	92%	92%	2	1	0.5
R7	AEX	FT	100	0	10	300	100	700	-	95%	95%	-	0.5	0.3
R8	MM	FT	150	0	10	375	100	3500	-	90%	90%	-	1.2	0.6
R9	MM	BE	50	1.4	26	100	100	1900	-	90%	90%	-	1.5	0.8
R10	MM	BE	35	1.4	26	250	12	2700	-	90%	90%	-	2	1
R11	HIC	BE	27.5	1.4	26	175	100	2500	-	89%	89%	-	2	0.5

Table 2
Chromatography column size candidates.

Decision	Candidate values
Bed height (cm)	15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25
Diameter (cm)	50, 60, 70, 80, 90, 100, 120, 160, 180, 200
Number of cycles	1, 2, 3, 4, 5, 6, 7, 8, 9, 10
Number of columns	1, 2, 3, 4

Table 3
Triangular probability distributions of uncertainty parameters.

Parameter	Lower bound	Peak	Upper bound
titre	2 (g/L)	3 (g/L)	4 (g/L)
cyd_s	95%	100%	105%
$lrvd_s$	80%	100%	120%

6. Results and discussion

In this section, the proposed optimisation model and solution approach are applied to the above case study. Then, the obtained optimal manufacturing strategies are examined through Monte Carlo (MC) simulation. At last, the sensitivity analysis of confidence level is conducted. All computational runs were implemented in GAMS 24.7 (GAMS Development Cooperation, 2016) on a 64-bit Windows 7 based machine with Intel Core i5-3330 3.00 GHz processor and 8.0 GB RAM, using CPLEX as MILP solver.

6.1. Optimal results

The proposed multi-objective optimisation model, MO–CCP, as well as the deterministic model, MO-DET, as the base case for comparison, are solved. The confidence level of chance constraint feasibility in the MO–CCP model is set to 95%, i.e., $A^t = A^y_s = A^l_s = 95\%$. With a 95% confidence level, $\Phi^{-1}(1 - A^t)$ in Eq. (7), $\tilde{\Phi}^{-1}_s(1 - A^y_s)$ in Eq. (11) and $\tilde{\Phi}^{-1}_s(1 - A^l_s)$ in Eq. (15) are approximately equal to 2.32, 96.58%, and 86.32%, respectively.

To implement the proposed solution approach, the minimum total LRV requirement of the purification process is initially set to 3.4 g/L, and then is gradually increased to 5 g/L ($TLRV^U$) with a step of 0.2 g/L ($\Delta TLRV$), and therefore a Pareto curve consisting of 9 Pareto-optimal solutions is obtained. The Pareto frontier of the MO–CCP model is compared with that of the MO-DET model in Fig. 3, where the optimal chromatography sequence of each Pareto-optimal solution is also presented. Table 4 shows the optimal chromatography column sizing decisions under each minimum total LRV requirement.

Firstly, the optimal chromatography decisions of the MO-DET problem are focused on. R5 (CEX) is selected at the capture step when the minimum required total LRV is low (<4), but R3 (AFF) with a higher standard LRV (3) is chosen when the minimum required total LRV increases, even it is much more expensive than R5. Meanwhile, R7 (AEX) is used for polishing at all optimal solutions. The actual total standard LRV of the whole process increases from 3.5 to 5.3, to meet the impurity removal capability requirement. As to the chromatography column sizing decisions, only one chromatography column is used at all steps in all solutions, while the other decisions vary, except that only the column with a diameter of 100 cm is always used at the capture step. With increasing minimum required total LRVs, COG/g increases by 10% from £68.4/g to £75.2/g.

Next, by comparing the solutions of MO–CCP to those of MO-DET, it can be seen that, for each minimum required total LRV,

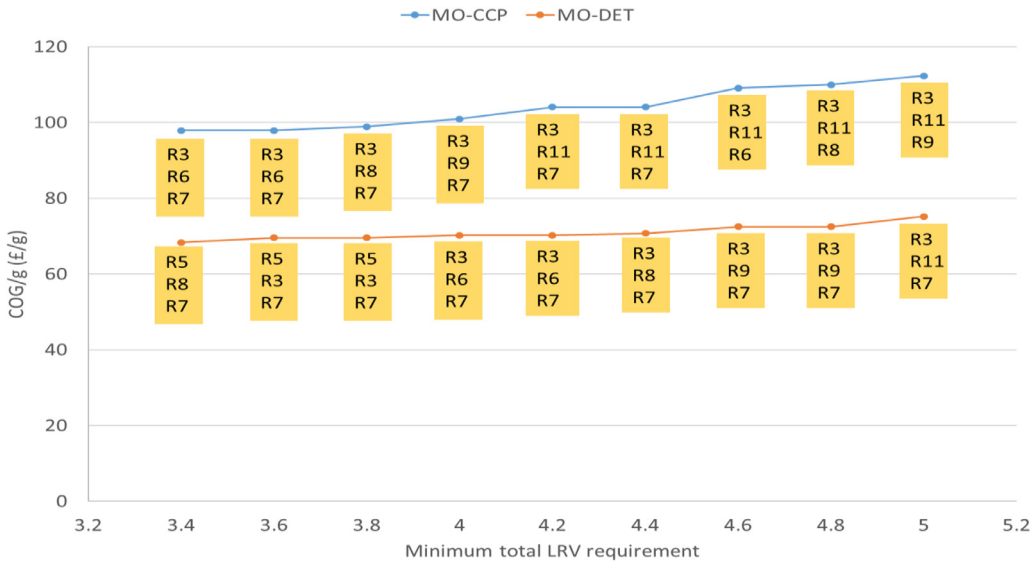

Fig. 3. The optimal COG/g and chromatography sequences of the MO–CCP and MO-DET models.

Table 4
Pareto-optimal solutions of the MO–CCP and MO-DET models.

	Minimum total LRV	Total standard LRV	COG/g (£/g)	Column diameter* (cm)	Column bed height* (cm)	No. of columns*	No. of cycles per batch*
Model MO-DET	3.4	3.5	68.4	100/50/70	15/15/17	1/1/1	4/10/6
	3.6	3.8	69.6	100/90/70	20/23/18	1/1/1	3/6/6
	3.8	3.8	69.6	100/90/70	20/23/18	1/1/1	3/6/6
	4.0	4.3	70.3	100/120/70	18/17/16	1/1/1	8/6/7
	4.2	4.3	70.3	100/120/70	18/17/16	1/1/1	8/6/7
	4.4	4.5	70.7	100/70/80	24/20/21	1/1/1	6/4/4
	4.6	4.8	72.5	100/160/60	18/23/21	1/1/1	8/2/7
	4.8	4.8	72.5	100/160/60	18/23/21	1/1/1	8/2/7
	5.0	5.3	75.2	100/180/70	16/22/18	1/1/1	9/3/6
Model MO–CCP	3.4	4.3	97.9	100/120/60	16/19/22	1/1/1	7/4/5
	3.6	4.3	97.9	100/120/60	16/19/22	1/1/1	7/4/5
	3.8	4.5	98.9	90/70/80	23/20/20	1/1/1	6/3/3
	4.0	4.8	100.9	100/200/60	16/22/18	1/1/1	7/1/6
	4.2	5.3	104.1	100/160/60	16/21/21	1/1/1	7/3/5
	4.4	5.3	104.1	100/160/60	16/21/21	1/1/1	7/3/5
	4.6	5.5	109.1	100/160/100	16/21/19	1/1/1	7/3/5
	4.8	5.6	110.1	100/160/50	16/21/17	1/1/1	7/3/6
	5.0	5.8	112.3	100/160/160	16/21/15	1/1/1	7/3/2

* values at capture/intermediate purification/polishing chromatography steps

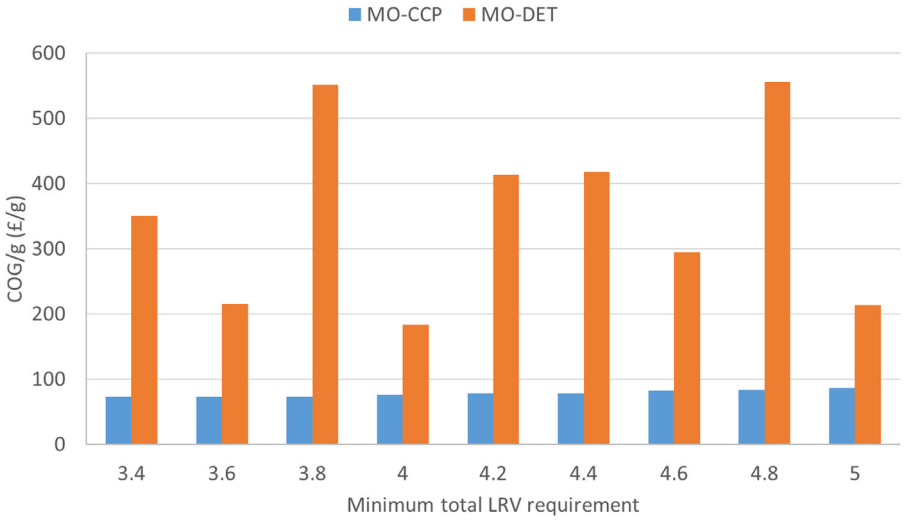

Fig. 4. Average COG/g in MC simulation on the solutions of the MO–CCP (95% confidence level) and MO-DET models.

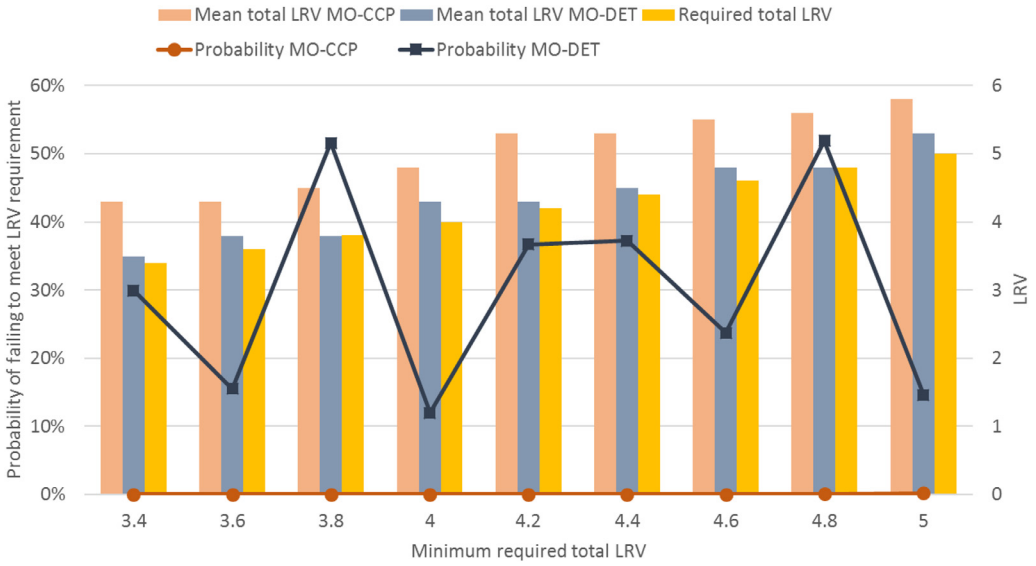

Fig. 5. Mean total LRVs and probabilities of failing to meet LRV requirement in MC simulation on the solutions of the MO–CCP (95% confidence level) and MO-DET models.

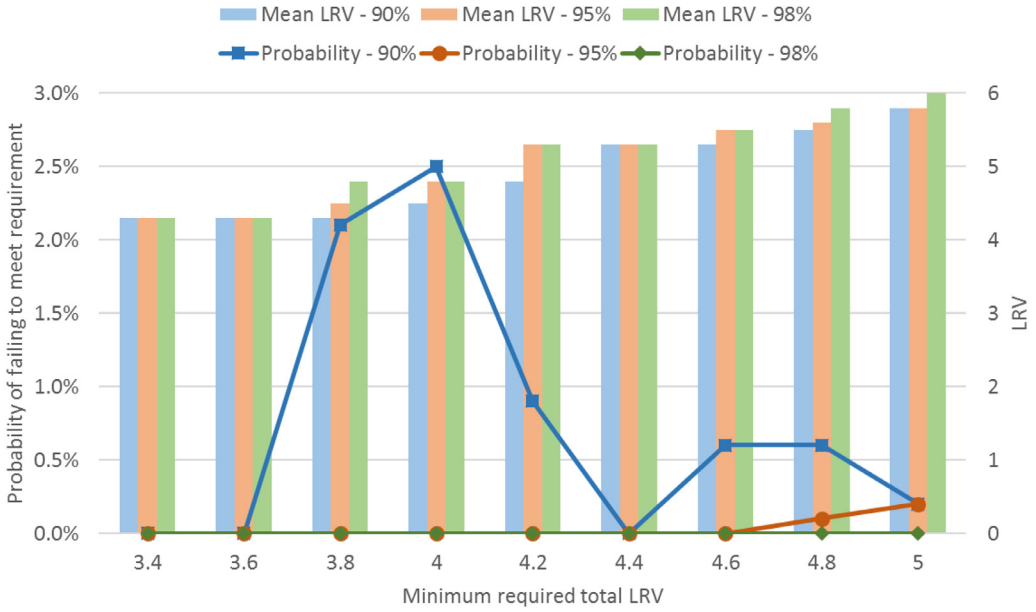

Fig. 6. Mean total LRVs and probabilities of failing to meet LRV requirement in MC simulation on the solutions of the MO–CCP model under confidence levels of 90%, 95% and 98%.

the MO–CCP model usually chooses a different chromatography sequence with higher total standard LRV than that of MO-DET model. For example, when the minimum required total LRV is 3.8, the MO–CCP model chooses a sequence of R3-R8-R7, which has a total standard LRV of 4.5, in order to guarantee that the realised total LRV is no less than the required level at the given confidence level (95%), while the optimal sequence of the MO-DET model, R5-R3-R7, has a total LRV of 3.8 only, which will fail to meet the requirement if the realisation is below expectation. Comparing the total standard LRVs in the solutions of two models, the sequence of the MO–CCP model is averagely 0.7 higher than that of the MO-DET model, and 0.8 higher than the minimum required total LRV. Moreover, the selected sequence of the MO–CCP model is also more expensive. Different from the solutions of MO-DET model, R5 is no longer a choice at the capture step, while R3 is used no matter whether the total LRV requirement is low or high. However, at the polishing step, although R7 (AEX) with relatively lower price and LRV is chosen in most cases, resins having higher LRVs are used when the impurity removal capability requirement increases. Due to the chance constraints on titre and yields, the selected column sizes of the MO–CCP model is smaller than the MO-DET model, leading to lower production. Similar to the deterministic case, the COG/g increases with increasing minimum required total LRV. Due to the higher cost and lower production, the obtained COG/g by optimising the MO–CCP model is over 40% higher than the MO-DET model. In the next section, we will conduct an analysis of MC simulation to highlight the benefits of the proposed CCP-based model.

6.2. MC simulation

Here, a stochastic analysis is conducted to examine the impact of variability on the solutions by implementing MC simulation (Kroese et al., 2011). MC simulation analysis was implemented on the solutions obtained by both MO–CCP and MO-DET models. After

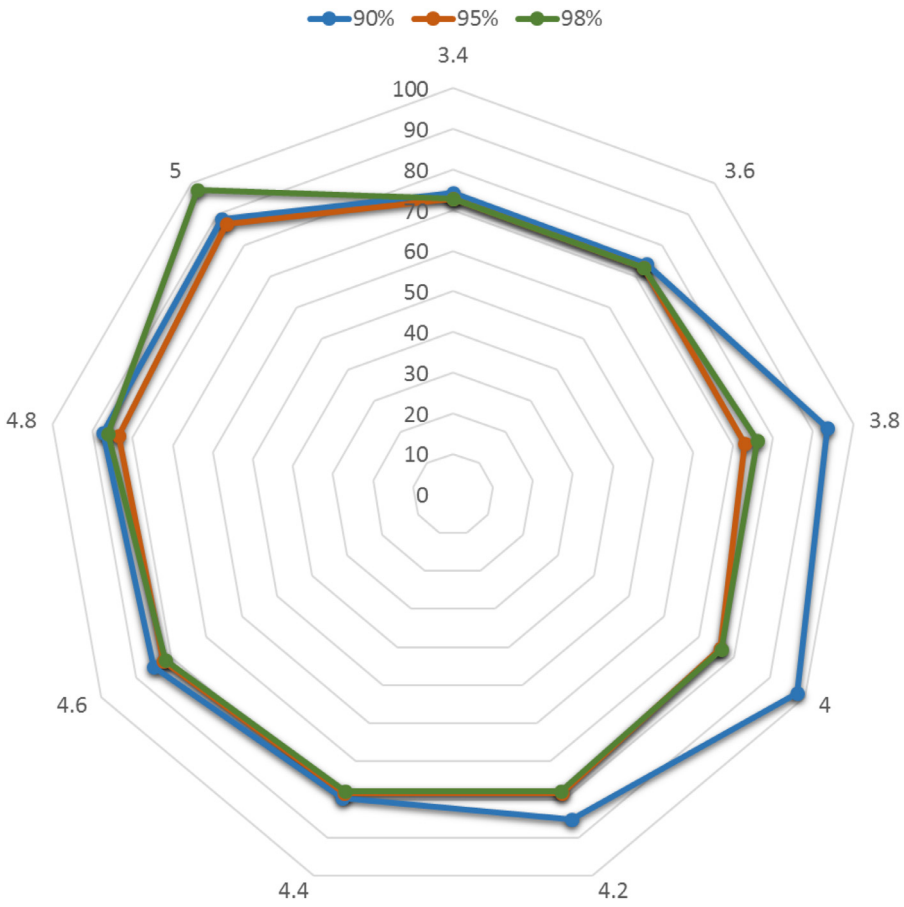

Fig. 7. Mean COG/g in MC simulation on the solutions of the MO–CCP model under confidence levels of 90%, 95% and 98%.

obtaining the optimal solutions of optimisation models, MC simulation analysis was conducted by solving the deterministic optimisation model, SO-DET, with fixed design variables, including variables for chromatography sequence, column volume and number of columns, to re-optimise all other operational variables, dependent on different realisations of uncertain parameters, *titre*, cyd_s and $lrvd_s$. In the proposed MC simulation, a total of 1000 simulation runs is implemented for each Pareto-optimal solution. Here, for the random realisation of each simulation run, it is firstly checked whether the realised total LRV meet the minimum required total LRV. If the realised total LRV is less the minimum required total LRV, the single objective optimisation model subject to the minimum required total LRV constraint is infeasible, and the final product of the generated purification process cannot meet the target purity level, which is treated as wastes. In this case, we take £1000/g as COG/g of this simulation run (Liu et al., 2016), which can be considered as the cost of outsourcing purchase. Otherwise, when the realised total LRV is no less than the minimum required total LRV, we run the deterministic model, SO-DET, to minimise the COG/g subject to the minimum total LRV and other constraints. The performance of the MC analysis is examined using the mean COG/g in all simulation runs, which mimics the expected value of COG/g. In addition, the probability of failing to meet the minimum LRV requirement is examined for the robustness of the selected chromatography strategies. The procedure of MC simulation is described as follows:

STEP 1. Fix the optimal chromatography sequences, column volumes and the number of columns obtained from the optimisation models;

STEP 2. Generate random titre, yield deviations and LRV deviations, all following triangular probability distributions as given in Table 4;

STEP 3. If the total LRV is lower than the minimum required total LRV, COG/g is set to 1000; Otherwise, solve the model SO-DET with the random parameters by the proposed solution approach in Section 4 to obtain the optimal COG/g;

STEP 4. Go to Steps 2 and 3 and repeat for 1000 times.

Fig. 4 shows the mean values of COG/g in the MC simulation. The mean values of COG/g in the MC simulation on the solutions of the MO–CCP model vary between £70/g and £90/g, which are lower than the optimal COG/g returned by the MO–CCP model, due to the underestimation of realisation of uncertain parameters in the chance constraints. Meanwhile, the mean values of COG/g in the MC simulation on the solutions of the MO-DET model are significantly higher by one order of magnitude, up to £560/g. Fig. 5 shows another benefit of the solutions MO–CCP model. The mean values of total LRV in the simulation on both MO–CCP and MO-DET models' solutions are same as the total standard LRVs obtained by the optimisation models, as reported in Table 4, which are all no less than the corresponding minimum required total LRVs. For the MO-DET model, the mean total LRV from the simulation is not significantly higher than the minimum required total LRV, with a difference of 0.3 at most and 0.1 on average. Therefore, the realised total LRV has a lower chance to meet the LRV requirement. For 9 Pareto-optimal solutions, the probabilities of total

LRV being lower than requirement are all greater than 10%, and the probabilities for two solutions are even more than 50% when the mean total LRV is the same as the minimum required value (3.8 and 4.8). In the meantime, the solutions of MO–CCP model obtain chromatography sequences with much higher total LRVs, at least 16% higher than the required values. Thus, there are just few simulation runs whose realised total LRV is less than the minimum required total LRV, and the probability of failing to meet the requirement is 0% except for two solutions. When the minimum required total LRV is high (4.8 and 5), only 1 or 2 simulation runs out of 1000 cannot meet the requirement. The relatively higher total LRV and lower probability of not meeting required purity level lead to the advantage of the solutions of the MO–CCP model. With smaller COG/g and lower failure rates, the MO–CCP model shows higher robustness, compared to the MO-DET model, to deal with the uncertainties in titre, resin yield and impurity removal capability.

Overall, the proposed MO–CCP model is able to cope with the uncertainties of the parameters, i.e., titre, resin yields and LRVs in this problem, to achieve significant economic benefits than the deterministic counterpart.

6.3. Sensitivity analysis of confidence levels

In the proposed CCP-based model, the confidence levels in the chance constraints impact the probabilities of the solutions being feasible. A risk-averse decision with a higher confidence level makes the chance constraint to be held with higher probability. Here, it is assumed that the same confidence level is implemented in all chance constraints. Three different confidence levels, 90%, 95% and 98%, are considered in this section. The optimal solutions obtained by the proposed MO–CCP model are examined using the MC simulation as described in the previous section. The details of the obtained optimal solutions with the 90% and 98% confidence levels are provided in the Supplementary Material (Tables S4 and S5). In order to cope with low LRV realisation, the optimal solutions with higher confidence levels select chromatography sequences with higher total LRV, which are also more expensive, and incur lower probabilities of being lower than the requirement, as shown in Fig. 6. When the confidence level is 90%, the total LRVs of the chromatography sequence in the optimal solutions are smaller than the other two, and there are 6 solutions (out of 9) whose simulation runs cannot meet total LRV requirement, although the probability is quite low, only up to 2.5%. For the confidence level of 98%, the selected sequences have the highest total LRVs, and the simulation runs of all solutions generate higher total LRVs than the minimum requirement.

Consequently, as presented in Fig. 7, a confidence level of 90% achieves higher mean COG/g than the other two, except when the minimum required total LRV is 5, much more expensive resins are selected under the conference level of 98%, resulting in higher COG/g. The COG/g in the simulation under the conference levels of 95% and 98% are comparable to each other. It can be observed that the achieved mean values are quite similar. When the minimum required total LRVs are high (4.8 and 5), the confidence level of 95% gets slightly smaller mean COG/g than the conference level of 98%, but has higher chance not to meet the minimum total LRV requirement. Especifically for this problem, confidence levels ranging from 95% to 98% are applicable to chance constraints for high quality solutions.

7. Concluding remarks

This work addressed the multi-objective optimisation of downstream processing of mAb products, to find the optimal chromatography sequencing and column sizing strategies. Both cost and impurity removal capability of the purification process are considered as objectives. Considering uncertainties in bioreactor titre, chromatography yield and LRV of HCPs, a stochastic CCP-based multi-objective optimisation model has been developed by extending previous work (Liu et al., 2014). To solve the proposed model, ε-constraint method and Dinkelbach's algorithm have been adapted to develop an iterative solution approach to generate a set of Pareto-optimal solutions with different minimum required total LRVs of the whole process. An industrially-relevant example has been investigated. The computational results of 9 Pareto-optimal solutions have shown that the CCP-based model deals with the variability of uncertain parameters in a better manner than the deterministic model, through the valuation of MC simulation, obtaining much less mean COG/g. Also, a sensitivity analysis on the confidence level shows the effects on the selected resin LRVs and COG/g in the MC simulation.

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Supplementary material

Supplementary material associated with this article can be found, in the online version, at 10.1016/j.compchemeng.2018.09.015

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