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Mathematical programming approaches for downstream processing optimisation of biopharmaceuticals

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ABSTRACT

This work addresses the optimal downstream chromatography sequencing and column sizing strategies in the manufacturing processes of monoclonal antibodies (mAbs). A mixed integer linear fractional programming (MILFP) model is developed to achieve continuous bed height values. In addition, to ease the computational expense of the literature MILFP model for discrete bed height values, two efficient hierarchical solution approaches are developed involving the two MILFP models, in which, based on its optimal solution of the newly developed MILFP model, the reduced MILFP model is solved with smaller decision region to find the final solution. A Dinkelbach-based algorithm is used as the solution approach of the MILFP models. Finally, a case study with different upstream processing (USP) and downstream processing (DSP) ratios are investigated, and the results show that all proposed approaches have high computational efficiency to satisfy different needs of the decision makers.

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1. Introduction

Monoclonal antibody (mAb) therapeutics represent one of the fastest growing sectors in the biopharmaceutical industry, whose global sales in 2011 were estimated at 44.6 billion USD and predicted to increase to 58 billion USD by 2016 (Butler, 2013). With the increasing mAbs demand and market competition, significant attention is being focused on reducing manufacturing costs and improving process efficiency for industrial-scale production (Mehta et al., 2008). In a typical manufacturing process of the mAb, mammalian cells expressing the mAb are cultured in the upstream processing (USP), and the mAb is recovered, purified and cleared from viruses by a variety of operations, including a number of chromatography steps, in the downstream processing (DSP). The chromatography purification steps are critical to the whole manufacturing process in terms of the cost and productivity. The chromatography steps are key steps to separate the protein of interest from the mixture, and have significant impact on the purity of the final product. Because of the expensive chromatography resins and the large amount of buffer used, they usually comprise of a large portion of the total manufacturing cost, and the cost-effectiveness of a mAb manufacturing process depends on the decisions on the chromatography strategies. Nowadays, with the increased titre in the USP, the chromatography steps need to tackle with the increased protein loaded in a time- and cost-efficient way, which becomes a bottleneck in the DSP.

Computer-aided decision tools have been used to assist decision making in the mAb manufacturing process, especially in the DSP (Lim et al., 2005, 2006; Stonier et al., 2012, 2013; Pollock et al., 2013a,b). In addition, a number of optimisation-based approaches have been developed in the literature work recently. Evolutionary algorithms (EAs) have received much attention on this topic. For example, Simaria et al. (2012) developed a meta-heuristic optimisation approach using EAs,

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focusing on the optimal purification sequences and chromatography column sizing strategies. Allmendinger et al. (2012, 2014) addressed an industrially relevant problem concerned with the discovery of cost-effective equipment sizing strategies for purification processes, which was modelled as a combinatorial closed-loop optimisation problem and solved by EA. Meanwhile, mathematical programming models have been developed in the literature. Liu et al. (2013a) addressed the chromatography column sizing decisions, including column diameter, bed height, number of columns and number of cycles, in the mAb manufacturing, and developed a mixed integer linear programming (MILP) model with an objective to minimise cost of goods per gram (COG/g). Later, in Liu et al. (2013b), a mixed integer nonlinear programming (MINLP) model was proposed for the facility design with the current titre. Then, the titres were increased, and parts of the column sizing decisions were re-optimised to fit the equipment from the facility design. In the recent work of Liu et al. (2014), the integrated chromatography sequencing and column sizing strategies of the mAb purification process were addressed. Besides the column sizing decisions, the chromatography sequence, i.e. the resin used at each chromatography step, is determined as well. To solve this problem, an MINLP model was developed, which was reformulated as a mixed integer linear fractional programming (MILFP) model using exact linearisation techniques. An algorithm based on the classic Dinkelbach's algorithm (Dinkelbach, 1967) was used to solve the MILFP model, which was proved to be much more efficient than solving the MINLP model. Although the CPU time is significantly reduced through the case study investigated in Liu et al. (2014), the problem size investigated there is quite small, with only 6 resins as candidates. However, in the real world problem, the number of the candidate resins can be much larger. In this case, the computational performance and ability of the proposed MILFP model should be further investigated.

The above work treated the bed heights as discrete integer values, which could also take continuous/decimal values in real practice. Thus, the aim of this work is to extend the work of Liu et al. (2014), and develop a new MILFP model which takes continuous values of the bed heights. Also, based on the new MILFP model, we develop efficient solution approaches to find discrete bed heights to overcome the computational difficulty of literature MILFP model for large instances.

The rest of this paper is organised as follows: In Section 2, by investigating an industrially relevant motivation example, the limitation of the literature MILFP model and the motivation of this work are shown. Then, the problem statement is presented in Section 3. The mathematical formulation of a new optimisation model is presented in Section 4, followed by two hierarchical solution approaches proposed in Section 5. The computational results of the proposed approaches on the industrially relevant example are presented and discussed in Section 6. Finally, the concluding remarks are made.

2. A motivation example

In this section, we investigate an industrially relevant motivation example of mAb manufacture with a typical manufacturing process (as shown in Fig. 1). There are 20 candidate commercial resins to be selected for purification at the chromatography steps (purple in Fig. 1). These resins are from 4 types, including affinity (AFF), cation-exchange (CEX), anion-exchange (AEX), and mixed-mode chromatography (MM), and present trade-offs in key operating characteristics (e.g. dynamic binding capacity and linear velocity). The key characteristics of the resin candidates that impact the performance metric of the downstream process are shown in Table 1. Each resin's lifetime is 100 cycles. Similar to the example discussed in Liu et al. (2014), we have 11 discrete potential bed heights (ranging from 15 cm to 25 cm) and 10 discrete potential column diameters (ranging from 50 cm to 200 cm). Meanwhile, at most 10 cycles per batch are allowed, while up to 4 parallel columns are permitted at each chromatography step. All other parameters of the example are the same as the example discussed in Liu et al. (2014).

In the work of Liu et al. (2014), an MILFP model was developed for the optimisation of the downstream chromatography sequencing and column sizing strategies, to minimise COG/g, which is equal to the annual total cost (*AC*) divided by the annual total production (*AP*). The binary variables are introduced for the selection from the discrete column volumes, determined by discrete column bed heights and diameters, in the developed MILFP model, which is denoted as MILFP_DBH model in this paper. In the literature work, there are a few solution approaches for mixed integer fractional programming models, e.g. Dinkelbach's algorithm (Bradley and Arntzen, 1999; You et al., 2009; Zhong and You, 2014) and reformulation-linearisation method (Yue et al., 2013). An algorithm based on Dinkelbach's algorithm was adapted by Liu et al. (2014), in which the MILFP model is solved by solving a sequence of MILP models iteratively, as presented in Fig. 2. In this Dinkelbach-based algorithm, each MILP model is solved with an optimality gap <100%, then the global optimum of the MILFP model is guaranteed.

In order to find the optimal chromatography sequencing and column sizing strategies of the mAb manufacturing, we apply the above Dinkelbach-based algorithm to the industrially relevant example, where three scenarios with different USP and DSP train ratios, i.e. 1USP:1DSP, 2USP:1DSP and 4USP:1DSP, are considered. The corresponding bioreactor volume of each scenario is 25,000 L, 12,500 L, and 6250 L, respectively. Here, more USP units will lead to smaller batch size and has tighter DSP windows, while fewer USP units will result in fewer number of batches. The models and approaches are implemented in GAMS 24.0 (Brooke et al., 2012) on a 64-bit Windows 7 based machine with 3.20 GHz six-core Intel Xeon processor W3670 and 12.0 GB RAM, using CPLEX MILP solver with four threads. Based on the discussion in Liu et al. (2014), the optimality gap for a single MILP model in the algorithm does not affect the optimality of the algorithm, as long as it is less than 100%. Since the Dinkelbach-based algorithm is quite robust with respect to the optimality gap, we set it to 10% in this work. The CPU time limit for a single MILP model is 10 h.

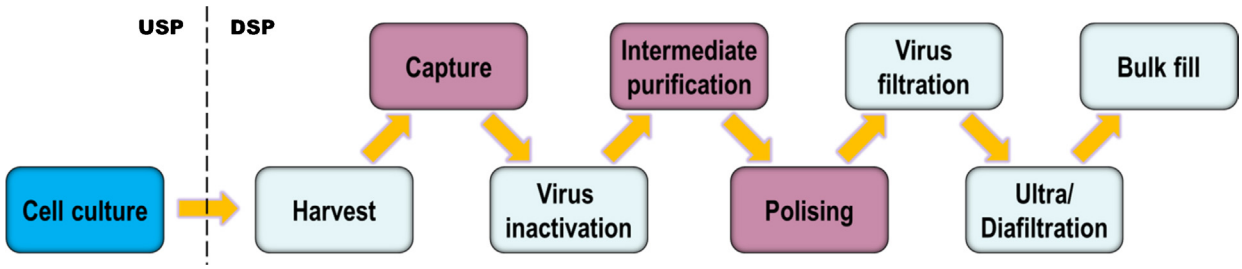

Fig. 1 – A typical mAb manufacturing process.

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