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Multiobjective evolutionary optimization in antibody purification process design

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ABSTRACT

To contribute towards designing more cost-efficient, robust and flexible downstream processes for the manufacture of monoclonal antibodies (mAbs), a framework consisting of an evolutionary multiobjective optimization algorithm (EMOA) linked to a biomanufacturing process economics model is presented. The EMOA is tuned to discover sequences of chromatographic purification steps and column sizing strategies that provide the best trade-off with respect to multiple objectives including cost of goods per gram (COG/g), robustness in COG/g, and impurity removal capabilities. Additional complexities accounted for by the framework include uncertainties and constraints. The framework is validated on industrially relevant case studies varying in upstream and downstream processing train ratios, annual demands, and impurity loads. Results obtained by the framework are presented using a range of visualization tools, and indicate that the performance impact of uncertainty is a function of both the level of uncertainty and the objective being optimized, and that uncertainty can cause otherwise optimal processes to become suboptimal. The optimal purification processes discovered outperform the industrial standard with, e.g. savings in COG/g of up to 10%. Guidelines are provided for choosing an optimal purification process as a function of the objectives being optimized and impurity levels present.

1. Introduction

Among therapeutic biopharmaceutical drugs, monoclonal antibodies (mAbs) represent one of the fastest growing category due to their unique binding specificity to targets [1,2]. Over the past decade, significant improvements have been accomplished in mAb upstream processing (USP) with higher titres (beyond 5 g/L) [3] being achieved in cell culture. However, these improvements have not been matched in downstream processing (DSP) [4–6]. The goal of this work is to contribute towards designing more cost-efficient, robust and flexible downstream processes using a simulation and optimization-based framework.

An antibody purification process consists typically of three chromatography steps, as depicted in Fig. 1. In two-thirds of the cases, Protein A is used as the main capture step, followed by cation and anion exchange chromatography [7]. With resin costs being already one of the most significant contributors to purification costs [8,9] (and Protein A resin being over 30 times more expensive than some ion exchange resins [10]), an increase in titres transforms chromatographic operations to critical steps in a mAb purification process. The design of cost-effective purification processes can help address this challenge [6]. The design stage is further complicated by the fact that regulatory bodies expect biopharmaceutical companies to fully understand their manufacturing process and be able to establish a purification process that is robust and conforms to strict purity requirements [11]. To assist the process of tackling these challenges, presented here is an optimization-based framework linking an evolutionary multiobjective optimization algorithm (EMOA) with a biomanufacturing process economics model. The goal of the EMOA is to discover sequences of chromatographic purification steps, and sizing strategies adopted at each step, that provide the best trade-off with respect to multiple objectives including cost of goods per gram (COG/g), robustness in COG/g, and host cell protein (HCP) removal capabilities. The objectives are then computed by the process economics model, which simulates additional manufacturing challenges including uncertainties and constraints.

Previous work on optimizing chromatographic purification processes looked at, for example, reducing the number of chromatography steps employed [12,13], exploration of non-Protein

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Nomenclature

Indices

d	decision variable
i, i'	chromatography step
j	objective function
t	Monte Carlo trial

Bioprocessing parameters

Δb	bioreactor step size (L)
$\overline{B}$	maximum bioreactor size (L)
$\underline{B}$	minimum bioreactor size (L)
C	total manufacturing costs (£)
d_i	column diameter at chromatography step i (cm)
D	annual demand (kg)
η	robustness of a manufacturing process COG/g
h_i	column bed height at chromatography step i (cm)
HCP_{initial}	HCP level pre purification
$\sum_{\text{HCP LRV}}$	HCP log reduction of a chromatographic purification process
HCP^*	HCP target post purification
$HCPFinal_t$	HCP level achieved post purification at Monte Carlo trial t
k	number of chromatography steps in a manufacturing process
M_i	mass of product entering chromatography step i (g)
$n_{\text{CYC},i}$	number of cycles each column at chromatography step i is used for
$n_{\text{COL},i}$	number of columns operating in parallel at chromatography step i
N	number of Monte Carlo trials
$p(\text{meeting required purity})$	probability of meeting the target HCP^*
P	annual product output (kg)
PT_i	processing time of chromatography step i (h)
r_i	resin used at chromatography step i
r_i^i	Boolean variable indicating if r_i is permitted to be used at chromatography step i
r_i^{RT}	resin type of r_i
$r_{i,Y}$	yield of r_i
$r_{i,E}$	eluate volume of r_i
$r_{i,DBC}$	dynamic binding capacity of r_i (g/L)
$r_{i,HCP\,LRV}$	HCP log reduction of r_i
τ	average resin utilization across all chromatography steps
$titre$	product titre (g/L)
V_i	volume of resin available at chromatography step i (L)
Y	theoretical global yield of a manufacturing process

Optimization algorithm parameters

f_j	objective function
F	objective space
g	generation counter
G	maximum number of generations
H	search history
l	number of decision variables
m	number of objective functions
μ	population size
ϕ	set of problem-specific factors controlling uncertainties in the manufacture
S	integer variable pointing to a feasible sequence of chromatography steps
$\mathbf{x}$	solution vector
x_d	decision variable
X	feasible search space

A based purification processes [10,14–16], and, similar to this study, (intelligent) selection of chromatographic resins, potentially coupled with the optimization of column sizing strategies and/or operating conditions [17–24]. Some of these studies are based on real physical experiments (e.g. [17,10,14]), while others involve simulations only (e.g. [18,20,23,24]).

Different simulation-based frameworks have been applied to purification process design including ones based on mathematical programming [25–28], discrete-event simulation [29,30], and evolutionary algorithms (EAs) [22–24]. The framework to be adopted depends on the overall goal to be achieved, e.g. optimization vs simulation.

Whilst evolutionary algorithms (EAs) have been applied successfully to complex problems from different application areas [31], within the bioprocess sector, EMOAs have received little attention only. Previous work in chromatography design/optimization has focused, e.g. on the application of EMOAs to operating parameter tuning (e.g. column loading, flowrate and gradient length) of a single chromatography step so as to improve recovery yield, purity, and productivity [22]. The focus here is rather on optimizing "high-level" criteria relating to all chromatography steps (e.g. impurity removal capabilities and resin utilization) or the complete manufacturing process (e.g. COG/g and its robustness). Moreover, uncertainty is associated with global operating parameters including product titre and HCP product levels pre-chromatography, as well as with chromatography specific parameters, such as yield, dynamic binding capacity (DBC), eluate volume, and HCP removal capability. The goal is to utilize a variety of easy-to-understand visualization tools to gain understanding about the impact of uncertainty on manufacturing performance and trade-offs between the objectives.

The rest of this paper is organized as follows. The next section gives a detailed formulation of the framework including the uncertain and multiobjective purification process design problem, and the EMOA; the problem extends the single-objective problem considered in [23,24] with multiple objectives (some of which have not been considered in the literature yet) and uncertainty. Section 3 describes a case study on the production of mAbs that will be used to demonstrate the use of the framework. Section 4 presents and discusses the results obtained for the case study. The concluding section draws together the findings from the analyses and discusses directions for further research.

2. Model formulation

Fig. 2 shows a schematic of the framework used in this work for the design of antibody purification processes: an EMOA is used to create solutions $\mathbf{x}$ (in this case, a particular purification process consisting of a sequence of chromatographic resins and column sizing strategies) and guide the optimization procedure. The string representation of a purification process is encoded, and the purification process embedded into a feasible manufacturing process, which is then evaluated using a biomanufacturing process economics model; manufacturing uncertainties are accounted for using Monte Carlo (MC) trials. Objective values pertaining to $\mathbf{x}$ are recorded and fed back to the EMOA to be considered in the generation of future solutions.