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Modelling of industrial biopharmaceutical multicomponent chromatography☆

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A B S T R A C T

The development and validation of a chromatography rate model for an industrial multicomponent chromatographic bioseparation is presented. The model is intended for use in a process scenario to allow specific variables critical to product quality to be studied. The chromatography provides impurity clearance whilst producing a complex product composed of six closely related variants of a dimer protein therapeutic (~30 kDa), with their monomer subunits in a specific ratio. Impurity removal is well understood, however, achieving the correct monomer subunit ratio can pose a purification challenge. We utilise a stepwise approach to develop a model for studying the effect of feed material variability on product quality. Scale down experiments are completed to quickly generate data for estimating model parameters, before an iterative procedure is employed where the industrial process is used to refine parameters in a sequential manner, until model predictions exhibit satisfactory agreement with experimental data. Final model predictions were in good agreement with experimental product quality (within 3%). The results demonstrate how good understanding of an industrial process can help facilitate model development when an exhaustive description is not required, despite considering a chromatographic bioseparation with crude feed material and challenging purification objectives.

Keywords: Process systems modelling; Quality by design; Chromatography modelling; Hydrophobic interaction chromatography; Purification process development; Therapeutic protein

1. Introduction

Advances in healthcare over the past half century have been of immense benefit to the quality of life for an increasing world population. The rapid growth in protein therapeutics has played a key role in this, and is predicted to continue with several hundred clinical candidate proteins currently estimated in company pipelines (Kelley, 2009) of which many serve significant unmet medical needs (Shukla et al., 2007). However, despite several decades of effort to improve R&D efficiency and performance, the process for bringing a new biopharmaceutical product to market remains an expensive, time-consuming, and risky proposition (Lightfoot and Moscariello, 2004).

Chromatographic separations are the workhorse of therapeutic protein purification (Kelley, 2007), but their design and operation is a challenging task. An optimal, safe and economic process must be found quickly somewhere in an extremely large parameter space which simply cannot be explored in depth using traditional experimental methodologies. Downstream process development currently depends heavily upon empirical experimentation interpreted using heuristic knowledge to arrive at an acceptable process (Lightfoot and Moscariello, 2004). The amount of material available to work with is often limited, and the work must be completed within constricted timelines to meet time to market constraints. Furthermore, US Food and Drugs Administration

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Notation

C^m	mobile phase concentration (mg/ml)
C^{sp}	stationary phase concentration (mg/ml)
CF	compression factor
D_A	apparent axial dispersion coefficient (cm^2/s)
F	mobile phase flowrate (ml/min)
k_a	equilibrium constant
L	column length (cm)
N_C	number of components
N_p	number of theoretical plates
q_s	saturation capacity (mg/ml)
q	settled resin concentration (mg/ml)
t_0	retention time of an unretained small molecule (s)
t	time (s)
u	interstitial velocity (cm/s)
V_0	void volume (ml)
V_C	column volume (ml)
ϵ_T	total column porosity
Δ	peak width of an unretained molecule at half of the peak height
i	component identifier

(FDA) regulations require that the basic separation scheme is fixed prior to clinical trials, early on in the overall development process.

The FDA is now encouraging the use of quality by design (QbD) principles during process development and operation (US Food and Drug Administration, 2006). Key to a QbD approach is a thorough understanding of process inputs and their impact on performance, the relationship between the process and the products' critical quality attributes (CQA), and the association between the CQA's and a product's clinical properties (Jiang et al., 2010). The expected benefit from a QbD approach is an increase in the assurance of product quality, and in turn, the FDA will allow manufacturers greater flexibility to operate with lower regulatory burden, enabling continuous process improvement, as well as greater robustness.

Mechanistic modelling can be a useful tool for studying the impact of process parameters on process performance and product CQA's. Altering the values of process parameters may be difficult or even impossible to accomplish experimentally, e.g. feed stream composition, but is trivial in a model based approach. In addition, simulations can be completed quickly and efficiently which is valuable in an industrial scenario where time and material is often limited, and the fundamental knowledge gained by their application can be used to better understand, and reduce, processing risks.

The equations used to mathematically describe the chromatographic purification of proteins are well understood (e.g. Kaczmarski et al., 2001; Guiochon, 2002; Brooks and Cramer, 1992; Seidel-Morgenstern, 2004). The systematic development of a chromatographic model has been described for many different systems, including ion exchange (Melter et al., 2008), hydrophobic interaction (McCue et al., 2008; Nagrath et al., 2011), and protein A chromatography (Ng et al., 2012). The issue of efficient model calibration has been thoroughly addressed (Teoh et al., 2001; Persson et al., 2006; Susanto et al., 2006; Osberghaus et al., 2012a). Mechanistic models of chromatography have been successfully employed to simulate numerous case studies (Kaczmarski et al., 2002; Mollerup et al., 2007; Osberghaus et al., 2012b). In addition, there are useful examples of using chromatography models for optimisation (Degerman et al., 2006, 2007; Ng et al., 2012), scale up (Gerontas et al., 2010), design space characterisation (Degerman et al., 2009; Gétaz et al., 2013b), as well as robustness, uncertainty and sensitivity analysis (Jakobsson et al., 2005; Borg et al., 2013).

As a result of the progress in modelling chromatography that has been made over the last decade, systems with crude feed material, containing product, product-related impurities (e.g. oxidation, deamidation, acetylation, dimerisation), and process-related impurities (e.g. antifoam, DNA, protein, virus) have recently been considered (e.g. Gétaz et al., 2013a; Nfor et al., 2013). The complexity of the industrial feed material in these studies means that the model development procedures involve conducting an extensive range of detailed experiments which may not be suitable in certain scenarios. One such scenario in industry is where the majority of process development has already taken place, but there remains a desire to develop understanding of a key feature of a bioseparation. The experimental effort required to develop an exhaustive model may discourage a mechanistic modelling approach considering time and material constraints.

In this work, a chromatography model for predicting product quality in an industrial multicomponent bioseparation is developed and validated. The model is intended for use in a process scenario to allow specific variables critical to product quality to be studied. The chromatography utilises a hydrophobic interaction retention mechanism to purify a multicomponent product from a complex mixture of impurities. Process parameters were predefined prior to this work. Impurity removal is well understood and therefore a model description of this feature of the chromatography is not required. However, the step must also deliver the multicomponent product composed of six closely related variants of a dimer protein therapeutic (~30 kDa) with their monomer subunits in a specific ratio. Variability in the feed material poses a purification challenge, and consequently, there is a risk that the products' monomer subunit ratio will not meet product quality specifications incurring significant losses. Therefore, a model which can study product quality as a function of the load material concentration and composition is developed and validated in this work. A systematic procedure is used to determine key model parameter values, first using targeted experimental studies to quickly generate experimental data for estimation of model parameters, before employing an iterative procedure where laboratory scale column runs of the industrial process using real feed material are used to refine parameters in a sequential manner until model predictions exhibit satisfactory agreement with experimental data. We demonstrate how good understanding of an industrial process can facilitate model development, despite considering a chromatographic bioseparation with crude feed material and challenging purification objectives.

2. Problem description

The hydrophobic interaction chromatography (HIC) considered in this work is a complex separation with challenging purification objectives. The product of interest is a disulphide linked dimer protein molecule (MW = 30 kDa), comprised of two monomer subunits. Three variations of the monomer

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