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An MILP formulation for the synthesis of protein purification processes

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ABSTRACT

This paper presents a mixed integer linear programming (MILP) model for the optimal synthesis of chromatographic protein purification processes including the time line in which our target protein product is collected. The model is linearised using piecewise linear approximation strategies and tested on three example protein mixtures, containing up to 13 contaminants and selecting from a set of up to 21 candidate steps. The results are also compared with previous literature models attempting to solve the same problem and show that the proposed approach offers significant gains in computational efficiency without compromising the quality of the solution.

Keywords: Downstream processing; Protein purification; Mixed integer linear optimisation; Piecewise linear approximation

1. Introduction

Process chromatography has been the prime tool of the biotechnology industry over the last decades. Its development within the last 20 years resulted in a large rise of revenues of the major healthcare companies (Curling and Gottschalk, 2007). Although alternative bioseperation technologies are making their way in the market, process chromatography will remain the high resolution process for industries for the years to come (Przybycien et al., 2004).

Although chromatography has been around for decades, there is still a need for more efficient design and operation, since it has always been a major bottleneck for industry, because of its complexity and its high capital and operating costs (Ngiam et al., 2003). Downstream processing can account for up to 80% of the total manufacturing cost of the product (Lowe et al., 2001). This emphasises the need for new tools and strategies that can provide solutions for the challenge of downstream processing design (Nfor et al., 2008) which is also encouraged by the Food and Drug Administration (FDA) (FDA, 2009).

One of the major challenges to be addressed is the selection of the chromatographic steps employed in the purification process. In an average biochemical process, several chromatographic steps are required to achieve a product quality within confined specifications. However, biopharmaceutical companies usually operate in suboptimal conditions and for that reason, many efforts have focused on developing systematic approaches for the efficient design of process chromatography.

The first efforts focused on knowledge-based and heuristics (Ostlund, 1986; Asenjo et al., 1989; Wheelwright, 1989; Eriksson et al., 1991). However, these methods inherently hold the drawback of not determining the best solution because of the size of the design space. For this reason, many authors have tried to develop systematic methods in order to predict and optimise the different performance criteria (e.g. chromatographic steps) (Asenjo et al., 1989; Lienqueo et al., 1999; Lienqueo and Asenjo, 2000; Steffens et al., 2000). Later on, several authors developed mathematical models based mainly on mathematical programming. In Vasquez-Alvarez et al. (2001) and Vasquez-Alvarez and Pinto (2004), two MILP models were developed, utilising physicochemical properties of all components in the mixture, in order to synthesise the optimal flowsheet for a specified purity and recovery. More recently, mathematical models based on mixed-integer non-linear

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