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Optimal cut-times finding strategies for collecting a target component from overloaded elution chromatograms

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ABSTRACT

The determination of accurate cut-times plays an important role in the design and implementation of preparative chromatography. Modeling and optimization studies involving preparative isolation of target components from multi-component mixtures overwhelmingly depend on the target amount collected, defined by specific cut-times. The task of finding these times can be quite challenging for complex chromatograms of experimental or theoretical origin. In this study, two new alternate strategies to find optimal cut-times are introduced. Using simple linear and complex overloaded chromatograms, the performances of these new methods are compared with that an established technique based on evaluating local purities. To demonstrate the methods, concentration profiles were generated theoretically using empirical functions and the equilibrium dispersive model. The methods are compared in terms of their accuracy, speed, robustness and also their ability to find multiple fractionation intervals.

1. Introduction

Optimal isolation of a high purity target component from a multi-component mixture is of significant importance in the pharmaceutical and biochemical industries. Over the years, preparative chromatography has been increasingly used to isolate target components from multi-component mixtures.

Once a preparative chromatographic separation process is set up, subsequent focus is generally to optimize operational parameters to realize an economically attractive application (Guiochon, Shirazi, Felinger, & Katti, 2006). Based on the specific final goal, a multitude of objective functions can be defined for the optimization problem. Suitably selected performance indices facilitate quantitative evaluation of the quality and the cost of separation. Typical objective functions are the production rate and the recovery yield with respect to the target component. They strongly depend on the amount of substance collected at the column outlet, which in turn is critically influenced by the fractionation or cut-times of the chromatogram. By evaluating the separation performance indices for a desired target component, a number of theoretical studies have been carried out to analyze and compare the potential of different chromatographic configurations; including conventional batch operational modes (Damtew, Sreedhar, & Seidel-Morgenstern, 2009; Sreedhar & Seidel-Morgenstern, 2008), recycling chromatography (Lee & Wankat, 2009; Sreedhar, Damtew, & Seidel-Morgenstern, 2009) and continuous separation techniques (Kessler & Seidel-Morgenstern, 2006).

It is expedient to consider the isolation of a target component from a complex mixture as a ternary separation problem with the intermediately eluting component as the target. Hereby, the determination of two essential cut-times plays a crucial role. A fast and easy to implement algorithm to find these two optimal cut-times based on analyzing local purities of the target component was suggested by Shan and Seidel-Morgenstern (2004). The role of threshold concentrations and different so-called expansion strategies were elucidated. The goal in this study is to generalize and explore alternative approaches for finding optimal cut-times to isolate the intermediately eluting component from a ternary mixture. In this regard, two novel strategies are proposed, which are based on a discrete and a continuous approach respectively. Using three case studies involving symmetric peaks and complex overloaded chromatograms, the efficiency and accuracy of the methods suggested are compared. The multi-component chromatogram required for the analysis were generated using two theoretical concepts. In the first case, symmetric (linear) chromatograms

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were generated using simple empirical functions having definite integrals. The main advantage here being the possibility of an analytical solution for the amount of target collected. In the second case, more complex and realistic overloaded (non-linear) chromatograms were calculated by numerical solution of the equilibrium dispersive model (EDM) (Guiochon et al., 2006).

2. Theory

2.1. General optimization problem and solution strategies

The general process optimization of a chromatographic system can be represented as:

$$\max_{X} \quad f(X)$$

subject to

- system dynamics
- bounds on X
- other constraints (purity, yield, etc.)

The objective function $f(X)$ to be maximized is usually the production rate or the recovery yield of the target component or any other function representing the performance of the separation process. Here, the vector X represent a set of design and operating parameters which are to be optimized. An optimal set X^* is found by solving the optimization problem subject to a set of constraints. The constraints primarily involve system dynamics in the form of governing equations. These are typically the mass balance equations, boundary conditions, relationships defining the kinetic and thermodynamic effects. The next set of conditions appear as inequality constraints in the form of bounds on variables. Finally, a set of conditions representing the quality of separation may be imposed, e.g. purity and/or yield constraints.

The greatest challenge in solving an optimization problem of the kind given above stems from the system dynamics. Most of the models applied to quantify preparative chromatography contain sets of partial differential equations (PDEs) (Guiochon, 2002; Guiochon et al., 2006). Such optimization problems are known as PDE constrained optimization problems and forms an actively researched topic today (Hazra, 2010; Hinze, 2008).

The easiest and most widely practiced strategy to solve such PDE constrained problems is using a nested black-box approach (Biegler, Ghattas, Heinkenschloss, & van Bloemen Waanders, 2003). The technique involves a black-box model which takes inputs in the form of decision variables to solve the system of equations describing the system dynamics along with boundary conditions. The values of the objective function and constraints are then calculated from the solution (chromatogram) and returned as output of the black-box model. An external optimizer could then be used to manipulate the decision variables to maximize or minimize the objective function, without violating the constraints. It must be noted that in such a nested construct, the solution of the governing equations themselves are independent of the cut-times. Thus, given a chromatogram (solution of the system of PDEs), optimal cut-times could be estimated based on a fixed purity or fixed yield constraint, as described by Shan and Seidel-Morgenstern (2004). Thereby reducing the size of larger optimization problem by eliminating cut-times.

The optimizers used in the nested black-box strategy can be broadly classified into two types; gradient based and those based on heuristic approaches. The former involves computation of the gradient or the Jacobian of the objective function and constraints with respect to the decision variables (Biegler, 2010). There are a bunch of examples where gradient based methods have been used successfully to analyze chromatographic separations (e.g. Gao & Engell, 2005; Kawajiri & Biegler, 2006; Suwondo, Wilhelm, Pibouleau, & Domenech, 1993). The greatest advantage of gradient based optimizers is that the solution found is a certified optimum. A major drawback in this method is that any sort of discontinuities or disturbances in the objective function lead to non-convergent solutions.

The non-convergence due to discontinuities, etc. could be tackled by using gradient free heuristic optimizers. Examples in this category include genetic algorithm, simulated annealing, random search, etc. Most of the preparative chromatographic optimization studies carried out in literature have been done using non-gradient based approaches (Nagrath, Messac, Bequette, & Cramer, 2004; Sreedhar et al., 2009; Ziomek, Antos, Tobiska, & Seidel-Morgenstern, 2006; Ziomek, Kaspereit, Jezowski, Seidel-Morgenstern, & Antos, 2005). Unlike gradient based methods, the objective function here need not be continuous with respect to the decision variables. The major drawbacks of heuristic methods is that the solution found is not a certified optimum. In addition, heuristic algorithms may take a large number of iterations in order to find an acceptable solution.

The focus in this study is not the larger optimization problem, rather the accurate estimation of cut-times of an intermediately eluting component from a multi-component chromatogram. This cut-times estimation can be seen as a minor optimization problem, embedded within a much larger nested PDE constrained optimization problem. The advantages and pitfalls involved in finding cut-times using different methods and their compatibility with a larger optimization problem are explored in this work.

2.2. Construction of chromatograms

The suitable chromatograms required for our analysis could be constructed using empirical functions or could be obtained from analytical/numerical solutions of the underlying mass balance equations of a chromatographic column. The former are particularly useful for describing experimental chromatograms measured for diluted samples. Using only a few parameters, individual chromatographic peaks can be described with great accuracy by certain continuous functions. Over the years, many research groups have proposed an array of empirical functions capable of describing chromatograms with varying complexities. A review with over 90 examples is given by Marco and Bombi (2001). Many sets of the functions can be used for describing a variety of profiles including those characterized by peak asymmetry and tailing.

One such function is the well known three parameter Lorentzian (Cauchy) given by (Fraser & Suzuki, 1966; Pirogov, Obrezkov, & Shpigun, 1995):

$$C_i = \frac{h_i}{1 + 4((t - t_{r,i})/\sigma_i)^2} \tag{1}$$

where h_i,$t_{r,i}$ and σ_i are the three empirical parameters. Here, h_i represents the height of the peak, $t_{r,i}$ the retention time and σ_i characterizes the peak broadening. The main advantage of using such Lorentzian function is that it provides an analytical expression for its definite integral (Davies, 2008), representing an area under the chromatogram for a given integration interval. This value can be easily co-related to the amount of target collected. On the contrary, many alternative functions tabulated by Marco and Bombi (2001) do not have definite integrals.

One disadvantage of empirical functions is that their application is limited to chromatograms with distinct well-known characteristics (e.g. peak asymmetries, shock and tailing fronts). In contrast, multi-component preparative chromatograms could exhibit very complex shapes including asymmetries and multiple maxima. In such cases, interpolating functions could be effectively used for fitting non-standard shapes. Among such functions, cubic spline