Model-Based Determination of a Stationary Phase Gradient in Liquid Chromatography Using Optimal Control Theory

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Abstract

Several studies have shown that a stationary phase with a gradient of the ion exchange capacity or particle diameter can improve the column efficiency in liquid chromatography operating in gradient elution mode. However, no general method exists to obtain the optimal stationary phase gradient. This contribution closes this methodological gap by using optimal control theory. We combine control parametrization with a direct-single-shooting method to obtain optimal stratified stationary phases. We demonstrate our approach with an ion exchange chromatographic column. For the chosen case study, the optimal ion exchange capacity gradient predicts an increase of the separation efficiency by 36.3 % compared to a homogeneous column.

**Keywords**: optimal control, liquid chromatography, stationary phase gradient, efficiency

* 1. Introduction

In analytical liquid chromatography, the goal is to reach the most efficient columns possible. In general, homogeneous columns with constant properties in the axial direction are used. The required resolution is achieved by regulating the mobile phase composition, temperature, column length, or flow rate.

Nevertheless, using series-coupled columns with different properties has been established in recent years (Alvarez-Segura et al., 2016). The essential disadvantage of coupled columns is the additional void volume between the columns. Therefore, the concept of continuous graded stationary phases has been developed in several articles. Codesido et al. (2019) concluded that chromatographic packings with linear particle size gradients increase the efficiency compared to homogeneous packings. Note that we here use the established terminology in chromatography. The gradient here is not to be confused with the mathematical gradient of the profile but refers to the profile itself. Horváth et al. (2021) investigated convex and concave functions in addition to linear particle size gradients and found that convex gradients improve the column performance even more. In another contribution, Horváth et al. (2023) numerically investigated a gradient of an ion exchange chromatographic column.

However, there is no generally established method to actually design an optimal stationary phase gradient. We present a model-based approach that uses optimal control theory to determine an optimal continuous property of the stationary phase as a function of the axial position in the column.

* 1. Case study

We use an ion exchange chromatographic column to demonstrate that the presented method is highly effective. We aim to increase the retention time difference between two components by determining an optimal function of the ion exchange capacity in the axial direction . In order to describe the chromatograms of the two components at the outlet of the column, we use the equilibrium dispersive model in Eq. (1). For more information regarding the model equations, the reader is referred to Horváth et al. (2023).

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|  | (1) |

is the concentration of the corresponding component ; is the time variable; is the mobile phase velocity; is the axial dispersion coefficient. The retention factor of component is calculated by Eq. (2).

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| --- | --- |
|  | (2) |

is the internal column porosity; is the ion exchange selectivity of component ; is the charge of the solute ion of component . The eluent concentration is due to the gradient elution mode a function of time and axial position (Eq. (3)).

|  |  |
| --- | --- |
|  | (3) |

is the initial eluent concentration; is the parameter describing the constant slope of the gradient elution mode.

To solve Eq. (1), we need to formulate an initial condition and boundary conditions. At time , the column is filled with pure eluent and is flowed through by an inlet stream, which contains both components. From onwards, only pure eluent flows through the column. The outlet of the column is implemented as a constant flux. This results in the initial condition in Eq. (4) and the boundary conditions in Eq. (5) - (6).

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| --- | --- |
|  | (4) |
|  | (5) |
|  | (6) |

is the total length of the column; is the inlet concentration of component ; is the time point when the inlet stream changes to pure eluent; is the end time of the simulation.

* 1. Optimization criterion

The case study aims to maximize the separation of two components through an optimally chosen gradient of the ion exchange capacity . To reach the maximal separation, the retention time of the earlier eluting component can be minimized, and the retention time of the later eluting component can be maximized. Since increasing the retention time of the second component also increases the total analysis time, we want to prevent this solution by the formulation of the objective functional . Objective functional maximizes the separation of the two components , and an additional term becomes nonzero if the retention time exceeds the maximum allowable retention time . Moreover, we define a range of available minimal and maximal ion exchange capacities and .

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| --- | --- |
|  | (7) |
|  | (8) |
|  | (9) |
|  | (10) |
|  | (11) |

is the time point when the first component is fully eluted; is the time point when the second component reaches the outlet (cf. Figure 2).

* 1. Numerical solution

To obtain the chromatograms of the two different components, we need to solve the partial differential Eq. (1). The method of lines transforms Eq. (1) into a system of ordinary differential equations by discretizing the spatial variable using 200 equidistantly distributed discretization points. First-order partial derivatives are approximated using a two-point upwind scheme, and second-order partial derivatives are approximated using a three-point central scheme. The resulting system of ordinary differential equations is solved using ode15s in MATLAB (Version R2023a, supplier: The MathWorks, Natick, Massachusetts). The optimal control problem is reduced to a conventional optimization problem by combining control parametrization with a direct-single-shooting method (Goh and Teo, 1988). In the first iteration, it is assumed that the optimal function is linear. Therefore, the ion exchange capacities at the inlet and outlet are optimally determined, with all capacities linearly interpolated between these two points. In the second iteration, a third control variable is added in the middle of the first two. The three control variables are again optimally determined with continuous information linearly interpolated in between. With each iteration, one additional control variable is added between every two control variables. Using this strategy of successive refinement, any continuous function can be approximated. In this work, four iterations, and thus nine control variables are used to find the optimal function of the ion exchange capacity in the axial direction . The reader is referred to our previous contribution for detailed information regarding the optimal control algorithm (Eppink et al., 2023). The numerical gradient-based solver fmincon in MATLAB solves the resulting optimization problem. Table 1 specifies the model parameters chosen in the same range as in Horváth et al. (2023). The first value of the ion exchange selectivity , the charge of the dissolved ion , and the inlet concentration correspond to the first component, and the second value to the second component, respectively.

Table 1: Numerical parameters.

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| *Parameter* | *Value* |
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* 1. Results

The goal of the objective functional is to separate the two components as far as possible with a maximum retention time of the second component. Figure 1 shows the ion exchange capacity as a function of the axial position for the optimal column and the corresponding homogeneous column. The ion exchange capacity is minimal at the inlet of the optimal column and increases with increasing slope in the axial direction . Note that the optimal gradient of the ion exchange capacity is in good agreement with the results of Horváth et al. (2023).

The separation of the two components is much larger using the optimal column than the homogeneous column (Figure 2). The higher resolution of the optimal column is only due to the higher retention time difference between the two components and is not caused by minimizing physical bandwidth effects. Overall, the separation width is increased by 36.3 % using the optimal column compared to the homogeneous column. If no constraint is formulated in the optimization criterion, the solver would further increase the resolution by increasing the retention time of the later eluting component. However, this would lead to an overall higher analysis time and would not guarantee comparability between the optimal stationary phase gradient and the homogeneous column.



Figure 1: Ion exchange capacity as a function of the axial position for the optimal column and the homogeneous column.



Figure 2: Outlet concentration of both components over time for the optimal column and the homogeneous column with the same retention time .

* 1. Conclusion

Various works have already shown that a gradient of the stationary phase leads to an increase in the efficiency of a column in liquid chromatography in gradient elution mode. We are convinced that model-based methods like the one presented in this work will help to make the most of this advantage.

In this contribution, we presented a model-based method using optimal control theory to determine graded stationary phases in liquid chromatography in gradient elution mode. The optimal control algorithm obtained an optimal ion exchange capacity gradient as a function of the axial position in the column, which increases the separation efficiency of two components by 36.3 % compared to the homogeneous column with the same overall analysis time.

The transfer of the presented approach to different varying properties, such as particle diameter in any spatial direction, should be straightforward. Moreover, subsequent work could find the optimal gradient of the stationary phase in the spatial direction combined with determining the optimal gradient of the elution mode as a function of the time variable using optimal control theory.

One remaining challenge is the manufacturing of continuous graded columns. The further development of additive manufacturing tools may allow enhanced freedom of design in graded particle columns (Salmean and Dimartino, 2019). Moreover, graded ion exchange columns can, for example, be produced using electrostatic attachments of anion exchange latex particles with charge density gradients (Pohl, 2021).

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