



Adjoint-based estimation and optimization for column liquid chromatography models

Tobias Hahn^a, Anja Sommer^a, Anna Osberghaus^a, Vincent Heuveline^b, Jürgen Hubbuch^{a,*}

^a Karlsruhe Institute of Technology (KIT), Institute of Process Engineering in Life Sciences, Section IV: Biomolecular Separation Engineering, Karlsruhe, Germany

^b Heidelberg University, Interdisciplinary Center for Scientific Computing, Engineering Mathematics and Computing Lab, Heidelberg, Germany

ARTICLE INFO

Article history:

Received 2 August 2013

Received in revised form 14 January 2014

Accepted 21 January 2014

Available online 31 January 2014

Keywords:

Column chromatography

Inverse modeling

Optimization

Sensitivities

Adjoint method

ABSTRACT

Simulation and optimization of chromatographic processes are continuously gaining practical importance, as they allow for faster and cheaper process development. Although a lot of effort has been put into developing numerical schemes for simulation, fast optimization and estimation algorithms also are of importance. To determine parameters for an a priori defined model, a suited approach is the inverse method that fits the measurement data to the model response.

This paper presents an adjoint method to compute model parameter derivatives for a wide range of differentiable liquid chromatography models and provides practical information for the implementation in a generic simulation framework by the example of ion-exchange chromatography.

The example shows that the approach is effective for parameter estimation of model proteins and superior to forward sensitivities in terms of computational effort. An optimization of peak separation in salt step elution demonstrates that the method is not restricted to inverse parameter estimation.

© 2014 Elsevier Ltd. All rights reserved.

1. Introduction

Chromatography modeling has a long history in academia, as it fosters the understanding of the underlying physical and chemical processes. The potential of modeling for industrial applications is enormous. It ensures time- and material-efficient process development – if and only if the parameters for a chosen model can be determined with low sample consumption in short time.

In column liquid chromatography the sample is dissolved in a liquid (mobile phase) and flows through a packed bed of porous particles or a monolithic column (stationary phase). The physical or chemical properties of the stationary phase and the different components are utilized such that some components are retained more strongly than others. The mass transport through the column is described by modeling the fluid dynamics, while the retention of the species is described by empirical or (semi-)mechanistical models for adsorption, reactions, etc. (Michel, Epping, & Jupke, 2005). The most commonly employed models in liquid chromatography describe the mass transport in the column by so-called Convection-Diffusion-Reaction (CDR) equations, where the reaction term models phase transitions and eventually the retention

of the species. If no deeper insight into the retention mechanism is available, Langmuir-type models are often employed as sub-models for the reaction part, introducing at least two unknown parameters per component. With no a priori knowledge about the components' behavior, the inverse method is an attractive option, which alters parameters in a systematic fashion to achieve a match of measured chromatogram and model prediction. For some sub-models, such as the Steric Mass Action (SMA) model for ion-exchange chromatography of proteins (Brooks & Cramer, 1992), model calibration protocols exist (Brooks & Cramer, 1992), which allow for determining the component-specific parameters in a consecutive fashion. In a comparative study (Osberghaus et al., 2012a), this approach and the inverse method were found to reach equal prediction quality such that the latter is recommended for fast process development. For other modes of protein chromatography, e.g. hydrophobic interaction (HIC) and mixed mode chromatography (MMC), different types of models are available. They are partly based on thermodynamic approaches that involve hardly measurable quantities, e.g. for HIC (Mollerup, 2008) or MMC (Nfor et al., 2010). In these settings, inverse parameter estimation is the only available option. If several models come into consideration, model discrimination can be performed that depends even more on fast parameter estimation techniques.

Optimization algorithms for minimizing the error between simulation and measurements can be divided into deterministic

* Corresponding author. Tel.: +49 721 608 42557; fax: +49 721 608 46240.

E-mail address: juergen.hubbuch@kit.edu (J. Hubbuch).

and heuristic methods. Deterministic algorithms, such as steepest descent or Newton's method, can achieve local quadratic convergence rates by using derivative information, but might get trapped in local optima. When starting near the global optimum, they constitute the methods of choice. The problem of local optima is due to the non-linearity of most retention models. Heuristic algorithms can leave local optima by random jumps, but require a much larger number of model evaluations. This class includes genetic algorithms (Xu, Zhu, Xu, Yu, & Ray, 2013) or simulated annealing (Kaczmarski & Antos, 2006). A combination of deterministic and heuristic methods was studied in Xu et al. (2013). It represents a feasible approach in case of highly non-linear parameter dependencies.

To use a gradient-based deterministic algorithm like Newton's method, the gradients or *sensitivities* have to be computed for each unknown parameter. The *adjoint* or *backward sensitivity* method was presented earlier (James, Sepúlveda, Charton, Qui nones, & Guiochon, 1999) for an ideal model with the Langmuir isotherm equation. This algorithm solves an adjoint equation backwards in time, allowing to compute any parameter sensitivity by an additional integration involving the *adjoint* or *dual solution*. Later, the approach was considered to be complicated, difficult to derive, and error-prone (Forssén, Arnell, & Fornstedt, 2006), mostly because of the need for additional model-specific derivatives. Instead a refined finite difference approach was proposed, which computes the needed sensitivities by solving one additional problem in time per parameter. In a recent publication (Püttmann, Schnitter, Naumann, & von Lieres, 2013), this approach was applied to compute sensitivities with higher precision. Automatic differentiation was used to avoid manual errors, but adding such routines to an existing code requires thorough programming knowledge and particular insight into memory management when dealing with iterative solvers (Hascoët & Dauvergne, 2008). The achievable precision is higher compared to classical finite differences, but the computational effort is reported to be slower by a factor of 1.4 (Püttmann et al., 2013). It is arguable, whether highest precision is necessary throughout the whole estimation or optimization process. Especially when starting the iteration, faster computation is more important than exact intermediate derivatives.

For systems with a large number of component-specific parameters (e.g. for the target molecule, variants, fragments, aggregates, etc.), heuristic methods as well as forward sensitivity approaches may be computationally expensive and intractable. We hence derived a general formulation of the adjoint method for differentiable liquid chromatography models in the form of CDR equations, demonstrating that the derivation is manageable for a wide range of scenarios. The "error-prone" derivative calculation may be accomplished reliably with computer algebra systems or even online derivative calculators. We will comment on practical implementation and in particular on re-usability of the existing code. A practical example shows that the approach is effective and far superior to forward sensitivities in terms of computational effort.

The approach will be demonstrated for two test cases of SMA parameter estimation, first using four chromatograms of cytochrome *c* in different gradient elutions and second using three chromatograms of a mixture of cytochrome *c*, lysozyme, and chymotrypsin in different gradient experiments. In this study, no multiple local minimums were observed, but long drawn-out minimums skew to the model parameters (Fig. 3(a)), depending on the formulation of the SMA model equation. This may result in saddle points which cause the same problems as local minimums for algorithms only considering first-order sensitivities. To avoid the calculation of second-order derivatives, the problem of locally vanishing derivatives is mitigated by choosing a suitable formulation of the kinetic SMA isotherm equations, such that first order derivatives are sufficient for successful parameter estimation.

The adjoint method can also be used in optimization algorithms, for example to determine optimal process parameters occurring in the boundary conditions. The gradients of the objective function with respect to the involved parameters (pump speed, buffer/sample concentrations, etc.) can be computed using the adjoint method in the same way. An example shows the peak separation optimization of the ternary mixture by determining the optimal salt concentration for an elution step.

2. Theory

2.1. Chromatography models

A variety of models are employed depending on the phenomena occurring in the respective system, but most of them can be formulated using a common structure. Current models for column chromatography describe the changes of concentrations in three phases, the mobile phase concentration c , the pore phase concentration (mobile phase within the porous particles) c_p , and the stationary phase concentration q . Details on the derivation and an overview of models can be found in Michel et al. (2005), Guiochon, Shirazi, Felinger, and Katti (2006). In the following section, we will discuss models with the general structure:

$$0 = F_1(c, c_p) = F_{1,1}(c, c_p) \cdot c + F_{1,2}(c, c_p) \cdot c_p, \quad (1)$$

$$0 = F_2(c, c_p, q) = F_{2,1}(c, c_p, q) \cdot c + F_{2,2}(c, c_p, q) \cdot c_p + F_{2,3}(c, c_p, q) \cdot q, \quad (2)$$

$$0 = F_3(c_p, q) = F_{3,2}(c_p, q) \cdot c_p + F_{3,3}(c_p, q) \cdot q \quad (3)$$

where the terms $F_{m,n}$ are general operators in phase equation $m \in \{1, 2, 3\}$ that occur as pre-factor to a phase concentration c, c_p, q indicated by $n \in \{1, 2, 3\}$. The concentration variables are vectors containing quantities for all considered components, e.g. $c = (c_0, c_1, \dots)^T$.

Typically, the concentration transport in the column is assumed to be independent of the cross-sectional position, such that the interstitial concentration only depends on the time $t \in [0, T]$ and axial position $x \in [0, L]$ in a column of length L and is influenced by convection, diffusion, and interaction with the pore phase, e.g.

$$\begin{aligned} \frac{\partial c_i}{\partial t}(x, t) = & -u(t) \frac{\partial c_i}{\partial x}(x, t) + D_{ax} \frac{\partial^2 c_i}{\partial x^2}(x, t) \\ & - \frac{1 - \varepsilon_c}{\varepsilon_c} \frac{3}{r_p} k_{eff}(c_i(x, t) - c_{p,i}(x, t)) \end{aligned} \quad (4)$$

where u is the interstitial velocity, D_{ax} the axial diffusion coefficient ($(1 - \varepsilon_c)/\varepsilon_c)(3/r_p)k_{eff}$ a coefficient modeling the effective mass transfer rate with respect to the adsorbent particle radius r_p and column porosity ε_c . Several assumptions were made to consider the velocity and axial dispersion as constant, the most fundamental ones are a uniformly packed column, an incompressible liquid and a constant viscosity. For a detailed discussion we refer to Guiochon et al. (2006). In the nomenclature of Eq. (1), the terms $F_{1,1}$ and $F_{1,2}$ are

$$F_{1,1}(t) = \frac{\partial}{\partial t} + u(t) \frac{\partial}{\partial x} - D_{ax} \frac{\partial^2}{\partial x^2} + \frac{1 - \varepsilon_c}{\varepsilon_c} \frac{3}{r_p} k_{eff}, \quad (5)$$

$$F_{1,2} = -\frac{1 - \varepsilon_c}{\varepsilon_c} \frac{3}{r_p} k_{eff} \quad (6)$$

Download English Version:

<https://daneshyari.com/en/article/172363>

Download Persian Version:

<https://daneshyari.com/article/172363>

[Daneshyari.com](https://daneshyari.com)