



Fast and accurate parameter sensitivities for the general rate model of column liquid chromatography



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ABSTRACT

A fast and accurate solver for the general rate model is extended for computing sensitivities that describe the impact of small parameter changes on the simulated chromatograms. Parameter sensitivities are required by many optimization algorithms and are useful for understanding how chromatograms depend on specific system properties or operating conditions. They are efficiently computed with arbitrary precision by integrating a forward sensitivity DAE system that is derived from the original DAE system. The involved partial derivatives are either manually derived or computed by algorithmic differentiation. This approach is demonstrated to be more robust and faster for realistically sized problems, as compared to the traditional finite difference approach. Sensitivities are computed not only with respect to intrinsic model parameters, such as diffusion coefficients and isotherm parameters, but also with respect to parameters in the boundary concentrations, such as the slope of an elution salt gradient. The extended solver is part of the Chromatography Analysis and Design Toolkit (CADET).

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1. Introduction

Column liquid chromatography is among the most widely applied unit operations for downstream processing in biopharmaceutical industry (Carta & Jungbauer, 2010). Typical processes comprise several chromatography steps for concentrating, separating, and purifying product molecules from fermentation broth or natural sources (Subramanian, 2007). Chromatography modeling has a long tradition (Guiochon, Felinger, Shirazi, & Katti, 2006), and the well-known general rate model (GRM) describes mass transport of solute molecules at different levels of the chromatography column (Guiochon, 2002).

Abbreviations: AD, algorithmic differentiation; ADOL-C, automatic differentiation by overloading in C++; BDF, backward differentiation formula; CADET, Chromatography Analysis and Design Toolkit; DAE, differential-algebraic equation; FV, finite volumes; FD, finite differences; GPL, general public license; GRM, general rate model; IDA, implicit differential-algebraic solver; IDAS, implicit differential-algebraic solver with sensitivity capabilities; IVP, initial value problem; JUROPA, Jülich Research on Petaflop Architectures; MCL, multi-component Langmuir; MPM, mobile phase modifier; OpenMP, open multi-processing; PDAE, partial differential-algebraic equation; SMA, steric mass action; SUNDIALS, suite of nonlinear and differential/algebraic equation solvers; WENO, weighted essentially non-oscillatory.

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The GRM must be combined with suitable binding models for simulating different chromatography modes, for instance, affinity (Montesinos, Tejedamansir, Guzman, Ortega, & Schiesser, 2005), ion-exchange (Forrer, Butté, & Morbidelli, 2008), hydrophobic interaction (Xia, Nagrath, & Cramer, 2003), or mixed-mode (Nfor et al., 2010). However, interaction mechanisms of solute molecules and adsorber surfaces are still subject of active research, in particular, when additional parameters, such as ionic strength (Lan, Bassi, Zhu, & Margaritis, 2001), pH (Bankston, Dattolo, & Carta, 2010), temperature (Muca, Piatkowski, & Antos, 2009) and mobile phase modifiers (Degerman, Jakobsson, & Nilsson, 2007) are considered. Quantitative reproduction and prediction of industrially relevant separation processes also requires to account for several components or pseudo-components (Degerman et al., 2007).

Model simplifications, such as neglecting the mass transfer resistance caused by pore diffusion (Guiochon, 2002), can help to reduce the computational complexity and the number of model parameters. However, lumped parameters lose their physical meaning, and oversimplified models cannot be used for simulating scale-up and scale-down experiments when effects of scale-dependent and scale-independent mechanisms are lumped into the same model parameters. Consequently, modern chromatography models depend on increasing numbers of model parameters.

Model parameters are commonly estimated from measurement data by the so-called inverse method (Arnell, Forsén,

& Fornstedt, 2005). Calibrated models can then be applied for optimal experimental design (Pukelsheim, 2006) and (robust) process optimization (Degerman, Jakobsson, & Nilsson, 2006). All of these tasks typically require to minimize sums of squared residuals, and efficient optimization algorithms, such as the popular Levenberg–Marquardt algorithm (Levenberg, 1944; Marquardt, 1963), need derivatives of these residuals with respect to the estimated parameters.

Parameter derivatives, also referred to as sensitivities, can be computed by various methods. The finite difference approach is easy to implement but potentially tricky to apply as the ideal parameter perturbation is generally not known (Gill, Murray, & Wright, 1981; Li, Petzold, & Zhu, 2000). We have hence extended our GRM solver (von Lieres & Andersson, 2010) to computing parameter sensitivities by solution of forward sensitivity systems (Rabitz, Kramer, & Dacol, 1983). This method allows to efficiently compute parameter sensitivities with arbitrary precision by simply specifying the corresponding time integration tolerances, provided that the specific derivatives of the underlying partial differential-algebraic equation (PDAE) system can be accurately evaluated.

The major effort of extending our code to parameter sensitivities was spent for implementing exact derivative computations of the residual function F of the implicitly formulated PDAE system with respect to the state vector, y , to the time derivative of the state vector, \dot{y} , and to the parameter vector, p . The first two of these derivatives are identical with the original system Jacobian, $\partial F/\partial y$, and with the so called mass matrix, $\partial F/\partial \dot{y}$, for which analytical implementations are available from the existing code. Only the parameter derivatives, $\partial F/\partial p$, had to be newly implemented using operator overloading-based algorithmic differentiation (AD). The AD approach technically requires the same computational effort as first order finite differences, but computes the required derivatives with machine precision (Griewank & Walther, 2008).

2. GRM solver

We briefly review the basic characteristics and features of our forward GRM solver (von Lieres & Andersson, 2010). This code constitutes the basis for all extensions and enhancements that are presented in the forthcoming sections.

2.1. General rate model

The forward simulator solves the GRM of column liquid chromatography as derived and comprehensively discussed in Guiochon et al. (2006). The resulting PDAE system describes the unsteady mass transport by convection and dispersion in the interstitial column volume (Eq. (1)), and by diffusion within the porous beads (Eq. (2)). The state variables are interstitial concentration, $c_i(t, z)$, mobile phase concentration, $c_{p,i}(t, z, r)$, and stationary phase concentration, $q_i(t, z, r)$, of component $i \leq N_c$ at axial coordinate $z \leq L$, radial coordinate $r \leq r_p$, and time $t \leq T$. The model parameters are described in Section 5 (Tables 2 and 3).

$$\frac{\partial c_i}{\partial t} = -u \frac{\partial c_i}{\partial z} + D_{ax} \frac{\partial^2 c_i}{\partial z^2} - \frac{1 - \varepsilon_c}{\varepsilon_c} \frac{3}{r_p} k_{f,i} (c_i - c_{p,i}(\cdot, \cdot, r_p)) \quad (1)$$

$$\frac{\partial c_{p,i}}{\partial t} = D_{p,i} \left(\frac{\partial^2 c_{p,i}}{\partial r^2} + \frac{2}{r} \frac{\partial c_{p,i}}{\partial r} \right) - \frac{1 - \varepsilon_p}{\varepsilon_p} \frac{\partial q_i}{\partial t} \quad (2)$$

Several models for describing adsorption and desorption of solute molecules at the inner bead surfaces are implemented, including the multi-component Langmuir (MCL) model (Eq. (3)) (Müller-Späth et al., 2011), the steric mass action (SMA) model (Eqs. (4) and (5)) (Brooks & Cramer, 1992), and a mobile phase modifier

(MPM) model (Degerman et al., 2007). The mass balance equations (Eqs. (1) and (2)) must also be solved for the salt component ($i=0$) in the SMA model which is not present in the Langmuir model ($i=1, \dots, N_c$).

$$\text{MCL: } a \frac{\partial q_i}{\partial t} = k_{a,i} c_{p,i} q_{m,i} \left(1 - \sum_{j=1}^{N_c} \frac{q_j}{q_{m,j}} \right) - k_{d,i} q_i \quad (3)$$

$$\text{SMA } (i \geq 1): a \frac{\partial q_i}{\partial t} = k_{a,i} c_{p,i} \bar{q}_0^{v_i} - k_{a,i} d_{p,0}^{v_i} q_i \quad (4)$$

$$\text{SMA } (i = 0): \Lambda = \bar{q}_0 + \sum_{j=1}^{N_c} (v_j + \sigma_j) q_j; \bar{q}_0 = q_0 - \sum_{j=1}^{N_c} \sigma_j q_j \quad (5)$$

The quasi-stationarity indicator a can either be set to 0 or 1 in order to specify whether the binding models are solved as algebraic isotherm equations or as differential kinetic equations. Only the equilibrium constant, $k_{eq} = k_a/k_d$, is relevant for the quasi-stationary case, $a=0$, but not the absolute values of the adsorption and desorption constants. Hence, the desorption constant k_d can be set to 1 and the adsorption constant k_a to k_{eq} when $a=0$.

Danckwerts boundary conditions (Barber, Perkins, & Sargent, 1998) are applied at the column inlet and outlet (Eqs. (6) and (7)), a linear film-diffusion model is used at the outer bead boundary (Eq. (8)), and a symmetry condition is applied at the bead centers (Eq. (9)). Initial conditions and concentration profiles at the column inlet are described in Section 5.

$$\text{Column inlet: } u c_{in,i}(t) = u c_i(t, 0) - D_{ax} \frac{\partial c_i}{\partial z}(t, 0) \quad (6)$$

$$\text{Column outlet: } \frac{\partial c_i}{\partial z}(t, L) = 0 \quad (7)$$

$$\text{Bead surface: } \varepsilon_p D_{p,i} \frac{\partial c_{p,i}}{\partial r^2}(\cdot, \cdot, r_p) = k_{f,i} (c_i - c_{p,i}(\cdot, \cdot, r_p)) \quad (8)$$

$$\text{Bead center: } \frac{\partial c_{p,i}}{\partial r^2}(\cdot, \cdot, 0) = 0 \quad (9)$$

In contrast to the Langmuir model, which consists of ordinary differential equations (Eq. (3)), the SMA model also comprises an algebraic equation (Eq. (5)) for the salt component ($i=0$). However, a rapid equilibrium assumption, i.e. $\partial q_i/\partial t=0$ for $i \geq 1$, is sometimes applied to reduce the number of model parameters, and this assumption transforms all binding models to purely algebraic form.

2.2. Solution scheme

The PDAE system (Eqs. (1)–(9)) is discretized using the method of lines, i.e. the space coordinates z and r are discretized separately from the time coordinate t , resulting in a large system of coupled ordinary differential-algebraic equations (DAE). This DAE system is solved by a hierarchical scheme of nested iterations (left panel of Fig. 1):

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