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Effects of uncertainties in experimental conditions on the estimation of adsorption model parameters in preparative chromatography

Niklas Borg[a], Karin Westerberg[a], Niklas Andersson[a], Eric von Lieres[b], Bernt Nilsson[a,*]

[a] *Department of Chemical Engineering, Lund University, Lund, Sweden*
[b] *Institute of Bio- and Geosciences, IBG-1: Biotechnology, Forschungszentrum Jülich, Jülich, Germany*

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ABSTRACT

Model-based process design is increasingly popular when designing pharmaceutical purification processes. The effect of uncertainties in concentration measurements on the estimation of model parameters is analyzed for two cases of non-isocratic adsorption chromatography. A model, calibrated to experiments, is used to generate data by adding a Monte Carlo sampled error in the inlet concentrations. New model parameters are estimated by minimizing the deviation between the synthetic data and the model. The first case is a separation of rare earth elements by ion-exchange chromatography and the second case is a purification of insulin from a product-related impurity by reversed-phase chromatography. It is shown that normally distributed errors in the concentrations result in deviations in the UV-signal that are not normally distributed. With the applied method, known concentration distributions can be translated into probability distributions of the model parameters, which can be taken into account in the model-based process design.

1. Introduction

Preparative chromatography is an important separation technique in the pharmaceutical, biopharmaceutical and food industries (Guiochon, 2002). It is essential to find suitable operating conditions to ensure the purity of the product and to achieve high yields. Finding such operating conditions experimentally is time-consuming and labor-intensive, even with the available high-throughput techniques that can increase the amount of available experimental data (Treier, Lester, & Hubbuch, 2012).

Modeling is an effective tool for the analysis and design of preparative chromatography processes (Guiochon & Beaver, 2011) and several examples of model-based process design for biopharmaceutical applications have been published, see for example Kaltenbrunner, Giaverini, Woehle, and Asenjo (2007), Shene, Lucero, Andrews, and Asenjo (2006), and Karlsson, Jakobsson, Axelsson, and Nilsson (2004). The models applied here consist of partial differential equations describing the most important physical and chemical properties of the system. The concentration profiles in the axial column dimension and in the radial particle dimension are the driving forces for the mass transport, while the adsorption is driven by the equilibrium between the concentration in the dissolved phase and on the solid phase inside the particles. Common assumptions made when modeling chromatography are, for example, that there is no concentration gradient in the radial column dimension, and that all stationary phase particles are identical in morphology and size. These assumptions are generally considered to introduce negligible errors to the models for columns at lab-scale. Adsorption on the stationary phase is described by an equilibrium or kinetic model including parameters for the adsorption's dependency on aqueous concentrations and the properties of the solvent and the stationary phase.

Aside from any error caused by the model assumptions, the parameters in the model have to be estimated and are thus attributed with an uncertainty. The process model is normally calibrated to lab-scale experimental data, to reproduce the behavior in the studied system. A popular method to estimate the model parameters is the inverse method (Felinger, Alberto Cavazzini, & Guiochon, 2003; James, Sepúlveda, Charton, Quiñones, & Guiochon, 1999; Seidel-Morgenstern, 2004; Zhang, Selker, Qu, & Velayudhan, 2001). In the inverse method, experimental elution profiles are used to estimate the model parameters by minimizing the discrepancies between simulated elution profiles and the experimental data (Dose, Jacobson, & Guiochon, 1991). A least squares minimizer, using a quasi-Newton approach is often used to perform this estimation. While it is sensitive to the initial guess due to local minima, it requires relatively few simulations.

The inverse method is useful for fitting a simulation model which reproduces experimental data within the calibrated range. It does however require a priori selection of the model structure and that the properties of the experimental system are well known. Erroneous assumption of the experimental system properties may

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* Corresponding author. Tel.: +46 462228088.
E-mail address: bernt.nilsson@chemeng.lth.se (B. Nilsson).

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Nomenclature

Method

e	experiment
m_p	model with true parameters p
$m_{\hat{p}i}$	model with estimated parameters $\hat{p}i$
n	normalizing function
o_e	operating conditions in experiment
p	true parameters
$\hat{p}_i$	estimated parameters, sample i
x	true concentrations [mol m^{-3}]
$\hat{x}$	estimated concentrations [mol m^{-3}]
$\varepsilon_{x,i}$	error in estimated concentration [mol m^{-3}]
y_e	experimental data
$y_{m,p}$	model data using true parameters p
$y_{m,\hat{p}_i}$	model data using estimated parameters $\hat{p}_i$
$y_{s,i}$	synthetic data, sample i

State variables

c_i	desorbed concentration of component i [mol m^{-3}]
c_s	desorbed concentration of salt ion [mol m^{-3}]
$c_{t,i}$	concentration of component i in tank [mol m^{-3}]
$c_{t,i,in}$	inlet concentration of component i in tank [mol m^{-3}]
q_i	adsorbed concentration of component i [mol m^{-3}]
$q_{max,j}$	maximum adsorbed concentration of competing component j [mol m^{-3}]
t	time [s]
x_ε	volume fraction of ethanol
z	axial coordinate [m]

Model parameters

D_{ax}	dispersion coefficient [m^2 s^{-1}]
H_i	Henry coefficient in MPM of component i
$K_{eq,i}$	equilibrium coefficient in SMA of component i
N_c	number of competing components
$k_{kin,i}$	kinetic coefficient in of component i $[\mathrm{m}^{3\nu}\,\mathrm{mol}^{-\nu}\,\mathrm{s}^{-1}]_{\mathrm{SMA}}$ $[\mathrm{s}^{-1}]_{\mathrm{MPM}}$
u_i	linear velocity of component i [m s^{-1}]
γ_i	solvophobicity coefficient of component i
ε_c	interstitial porosity
$\varepsilon_{p,i}$	apparent porosity of component i
ν_i	characteristic charge of competing component j
σ_j	shielding factor of competing component j
Λ	ligand concentration in particle [mol m^{-3}]
τ	residence time in mixing tank [s]

Calibration method

RSS	residual sum of squares
N_{exp}	number of experiments
$N_{d,i}$	number of data points in experiment i
$UV_{exp,j,i}$	experimental UV data point j in experiment i [mAU]
$UV_{sim,j,i}$	simulated UV data point j in experiment i [mAU]
$\lVert UV_{exp,i}\rVert$	norm of experimental UV trace in experiment i [mAU]

Retention correlation

$V_{R,i}$	retention volume of component i [m^3]
$V_{NA,i}$	dead volume of component i [m^3]
V_{col}	volume of column [m^3]

introduce errors in the estimated model parameters. Sajonz (2004) and Samuelsson, Zang, Murunga, Fornstedt, and Sajonz (2008); Samuelsson, Fornstedt, and Sajonz (2008) have analyzed the quantitative effect of an error in the assumed hold-up time in the column on the Langmuir adsorption model parameters. By calibrating a model with erroneous hold-up time to a simulation with a true hold-up time, it was found that the erroneous hold-up times resulted in errors in estimated adsorption model parameters. Samuelsson, Fornstedt, et al. (2008) also showed the qualitative effect that a different adsorption model could give a better fit than the true adsorption model when an erroneous hold-up time was used. Other uncertainties in the model parameters can be an effect of variations in the experimental data. Joshi, Kremling, and Seidel-Morgenstern (2006) used synthetic adsorption equilibrium data to quantitatively determine the effects of concentration measurement error on adsorption model parameters. The synthetic data was generated by adding a Monte Carlo sampled absolute error to experimental equilibrium data. In Zhang et al. (2001), the quantitative effect of detector disturbance on the parameters of the multi-component Langmuir adsorption model was studied. The number of replicates needed to estimate the adsorption parameters within a specific confidence interval was determined by calibrating the model to data from simulations with an added Monte Carlo sampled relative error on the detected UV-absorbance signal.

The variations in experimental data do not necessarily appear as a bias in the detector. Hibbert, Jiang, and Mulholl (2001) analyzed the deviation of the UV-signal in analytical chromatography by adding a Monte Carlo sampled error to the experimental conditions in simulations. This showed that deviations caused by the experimental conditions, and not a noisy detection, can neither be modeled by an absolute, nor a relative random error. In order to understand the effect experimental errors have on the estimation of model parameters, this kind of the error must be analyzed.

Although the studies mentioned above are performed for isocratic conditions, preparative chromatography processes are often non-isocratic. Vivó-Truyols, Torres-Lapasió, & Garcĭa-Alvarez-Coque (2003) studied the effect of concentration uncertainty on explicit linear and quadratic retention model parameters for non-isocratic analytical conditions, but the effect of errors in the concentration measurements on the fitted model parameters of column models and for preparative conditions has not been studied before.

In this study we analyze the quantitative effect of uncertainty in the experimental conditions on the estimated chromatography model parameters for a non-isocratic, preparative process. A simulation model is used to generate synthetic data with Monte Carlo sampled experimental conditions, resulting in non-normally distributed errors in the elution profiles. The inverse method is then used to estimate the model parameters by fitting the model to the synthetic data, resulting in a distribution of the estimated model parameters.

Two cases are studied: Case 1 is the separation of rare earth elements (REEs) by ion-exchange chromatography. The model was calibrated to experimental data that has been presented by Ojala, Max-Hansen, Kifle, Borg, & Nilsson (2012). The experimental conditions studied are the total concentration of rare earth elements, the concentrations of acid in the buffers, and ligand density in the stationary phase. Case 2 is the removal of a product-related impurity from insulin by reversed-phase chromatography. Westerberg, Borg, Andersson, & Nilsson (2012) have previously described this model. The experimental variables studied in Case 2 are the concentration of ethanol, the concentration of protein, and the purity of the feed. The general outline of the method is presented first, followed by the experimental and computational details of the two cases. The effects of the experimental errors on the simulated chromatogram and on the estimated parameters are presented next, followed by a discussion of the implications for model calibration and the application of models in the design of preparative chromatography.