Methodology for model calibration of chromatography processes

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Abstract

The aim of this article was to improve the methodology for the model calibration of preparative chromatography processes using the simulation tool PCS and Gaussian curves designed in MATLAB. In the case studied the adsorption and desorption is based on Langmuir's kinetics and the mobile phase is a homogeneous model. The adaptation made for the calibration used EMG functions. To be able to optimize the calibration regarding the various parameters an object function was minimized by the minimization function *fminsearch* in MATLAB. One conclusion of the calibration was that it went well fitting Gaussian curves to the experiments and then calibrating the mechanistic model to the curves of the various components curves separately. However several more different experiments are needed to be able to verify the universality of the methodology.

Keywords: *Calibration, Preparative Chromatography, Gaussian curves, PCS, Simulation*

Introduction

With preparative chromatography the main focus is on the separation of different substances and this can be applied in several fields (Scott). It can be very beneficial to simulate a process when both time and money can be saved by reducing the number of expensive and extensive experiments needed. In this thesis preparative chromatography processes was simulated. This was done by using the mechanistic model from the PCS (Preparative Chromatograph Simulator) and MATLAB. By fitting Gaussian curves to the experiments first, separate curves for each component was obtained. The idea was to try and calibrate the model to those curves instead of calibrating it to the experiments directly.

Method

The PCS was used to simulate the chromatography experiments. The PCS is a simulation tool for simulation of different chromatography processes. The disadvantage of using this model is that if you want to get a good calibration of the experiments, this may take a long time. Gaussian curves were used in an attempt to shorten this time and try to predict how the individual components' curves in the chromatogram would be like.

Mechanistic Chromatography Model

In the case presented in this article the mechanistic model is based on a model called MPM (mobile phase modulator). The model is based on the Langmuir's kinetics as described in eq.1.

$$\frac{\partial q_i}{\partial t} = k_{kin,i}\left(\frac{S}{S_{ref,i}}\right)^{\nu_i}\left(H_i\left(\frac{S}{S_{ref,i}}\right)^{-\nu_i} e^{\nu_i\beta_i\left(S-S_{ref,i}\right)c_i}\left(1-\sum_j \frac{q_j}{q_{max,j}}\right)-q_i\right) \qquad \text{(eq.1)}$$

Where q is the concentration for a component on the stationary phase that changes per time unit t, S is the concentration for the acid, S_{ref} is the reference value for this concentration, γ is the

hydrophobicity for the component, v is the number of sites every ion is going to occupy on the stationary phase, k_{kin} is a kinetic constant and H_{ref} is a reference parameter that describes how well the components will adsorb on the surface at a specific pH. H_{ref} is proportional with q_{max} as described in eq.2.

$$H_{ref} = K_{eq} q_{max} \qquad \text{(eq.2)}$$

Where K_{eq} is a equilibrium constant as described in eq.3.

$$K_{eq} = \frac{k_{ads0}}{k_{des0}} \frac{\exp(-\gamma S_{ref})}{S_{ref}^{v}} \qquad \text{(eq.3)}$$

Where k_{ads0} and k_{des0} is kinetic constants that describes how fast the adsorption and desorption is happening.

The model for the mobile phase in this case is a homogenous model as described in eq.4.

$$\frac{\partial c_i}{\partial t} = D_{ax} \frac{\partial^2 c_i}{\partial x^2} - v_{int} \frac{\partial c_i}{\partial x} - \frac{(1-\varepsilon_c)}{\varepsilon} \cdot \frac{\partial q}{\partial t}$$
(eq.4)

Where the concentration c for each component changes with the time t. D_{ax} describes the axial dispersion, ε_c is the void in the column, ε is the total porosity, v_{int} is the velocity between the particles and x is the axial coordinate throughout the column.

Gaussian Curves

To generate Gaussian curves different functions could be used depending on the shape of the curve. To describe a symmetric curve without any skewness eq.5 was used.

$$y(t) = \frac{A}{\sqrt{2\pi}\sigma} \exp\left(-\frac{(t-t_R)^2}{2\sigma^2}\right)$$
(eq.5)

Where A is the area under the curve, σ is the width of the curve and t_R is the retention time (Felinger, 1998, s. 37).

To describe curves with skewness and therefore not symmetric EMG functions (Exponentially modified Gaussian functions) was used.

For the first order of EMG functions eq.6 and eq.7 was used.

$$For\ \tau > 0 \qquad y(t) = \frac{A}{2\tau}\alpha(\beta + 1)$$
(eq.6)

$$For\ \tau < 0 \qquad y(t) = \frac{A}{2\tau}\alpha(\beta - 1)$$
(eq.7)

For the second order of EMG functions eq.8, eq.9 and eq.10 was used.

$$For\ \tau_1 > 0, \tau_2 > 0$$

$$y(t) = \frac{A}{2(\tau_1 - \tau_2)}[\alpha_1(\beta_1 + 1) - \alpha_2(\beta_2 + 1)]$$
(eq.8)

$$For\ \tau_1 < 0, \tau_2 > 0$$

$$y(t) = \frac{A}{2(\tau_1 - \tau_2)}[\alpha_1(\beta_1 - 1) - \alpha_2(\beta_2 + 1)]$$
(eq.9)

$$For\ \tau_1 = \tau_2 = \tau > 0$$

$$y(t) = \frac{A\sigma}{\sqrt{2\pi}\tau^2} e^{\frac{(-t-t_R)^2}{2\sigma^2}} - \frac{A\alpha(\beta+1)}{2\tau}\left(\frac{\sigma^2}{2\tau} - \frac{t-t_R}{\tau}\right)$$
(eq.10)

In these equations τ represents the skewness. The variable α is describes in eq.11 and the error function with β is described in eq.12.

$$\alpha_i = \exp\left(\frac{\sigma^2}{2\tau_i^2} - \frac{t-t_R}{\tau_i}\right) \qquad \text{(eq.11)}$$

$$\beta_i = erf\left(\frac{t-t_R}{\sqrt{2}\sigma} - \frac{\sigma}{\sqrt{2}\tau_i}\right) \qquad \text{(eq.12)}$$

Object functions

The object function in this case calculates the difference between either the experiment curve and the Gaussian curve or the Gaussian curve and the model response. For this article the object function described in eq.13 was used.

$$res = \left(\sum_{i=1}^{n_{exp}} \left(\sum_{j=1}^{n_{points}} \left|c_{exp,j} - c_{sim,j}\right|\right)_i\right)^{1/2}$$

(eq.13)

Where c_{exp} is the concentrations for the experiment, c_{sim} is the simulated concentrations and *res* is the residual. The residual is the value the minimization function is minimizing to get the best fit.

Results and Discussion

The results in this article are based on three different experiments. The first two is duplicates with overlapping peaks and the third has a different lower gradient.

Fitting of Gaussian curves

It was pretty easy to get the max value on the y axis of the curves to be located accurate throughout the x axis in the chromatogram, but it was harder to get the width and the skewness accurate. By setting the initial value for t_R as the approximate maximum value of each component, a good start for the minimization function was acquired. By fitting Gaussian curves to several different experiments a good experience was acquired and a standard set of initial values was developed. With these a good fit could be acquired to other experiments faster. In Figure 1 an example of Gaussian curves can be seen.

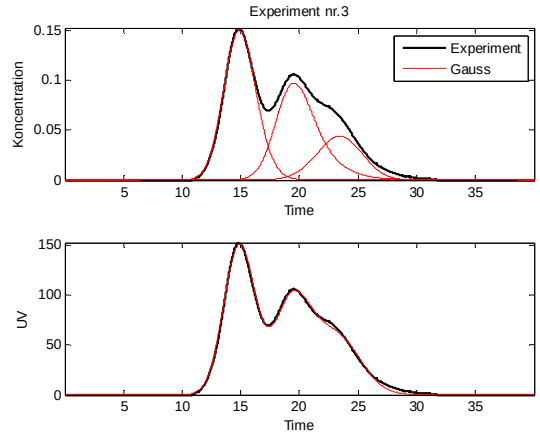

Figure 1 an example of how a fit of Gaussian curves can look like.

Calibration of the Mechanistic Model

With the mechanistic model as well as the Gaussian curves can be fit to each component and predict how these curves can look like.

In Figure 2 and Figure 3 a result of a fit of Gaussian curves to the experiment and a succeeding calibration of the model to the Gaussian curves can be seen.

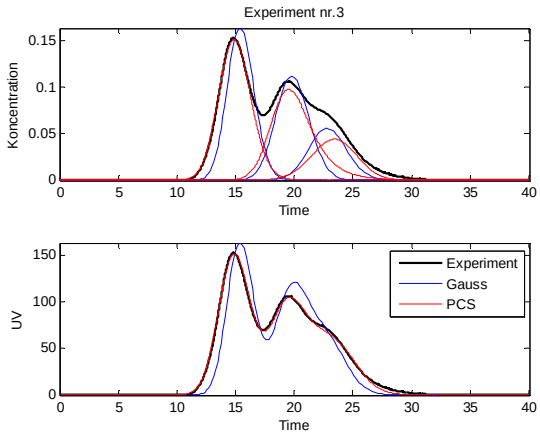

Figure 2 a manual calibration of the model without the minimization function to experiment 3.

In Figure 2 the calibration is not complete, as can be seen, and is only the initial guesses of the parameters for the model. The initial values does not have to be completely correct to get a good fit with the minimization function as can be seen in Figure 3. But the initial values cannot be too far away from the real values for the minimization function to be able to make a fit.

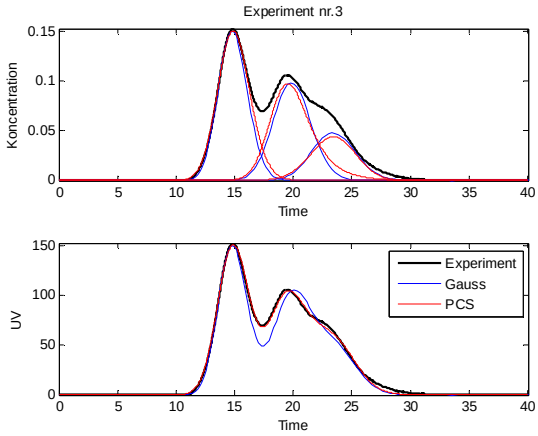

Figure 3 a calibration of the model with the minimization function to experiment 3.

As can be seen in Figure 3 double sources of errors exist in the calibration of the mechanistic model. This can be seen because the Gaussian curve is better fitted then compared to the model when comparing them with the experiment curve. This source of error occurs because the mechanistic model is not calibrated directly to the experiment but to the Gaussian curves and is therefore not connected to the experiments in first hand.

Conclusion

The fitting of the Gaussian curves to the experiment and the calibration of the mechanistic model has gone as expected. What hasn't gone as hoped is the improvement of finding better initial guesses. This of course needs to be further researched to be able to make the calibration even faster and easier.

The complete calibration method with fitting of Gaussian curves to the experiment and with succeeding calibration of the mechanistic model cannot be assumed to be valid in general when too few experiments have been applied. Further work on this project should include a wider variety of experiments that the analysis and calibration can be based on.

References

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