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Modelling and validated simulation of solvent-gradient simulated moving bed (SG-SMB) processes for protein separation

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Abstract

Continuously operated chromatographic processes like the Simulated Moving Beds (SMB) are well established for the purification of hydrocarbons, fine chemicals as well as pharmaceuticals. With respect to discontinuous batch chromatography they have proven their ability to improve the process performance in terms of productivity, eluent consumption and product concentration especially for larger production rates. These processes are operated under isocratic conditions where the composition of the mobile phase remains constant. Non isocratic processes are necessary if e.g. bio-products like proteins with a large difference in their affinity have to be separated. Therefore the implementation of solvent gradients is an important approach to improve the performance of SMB processes. The advantages of solvent gradient SMB processes are achieved by a higher complexity with respect to layout and operation which makes an empirical design nearly impossible. Therefore process simulation based on validated rigorous models is necessary for process design and optimisation.

Keywords: chromatography, simulated-moving-bed (SMB), solvent-gradient, protein-separation

1. Introduction

A SMB unit consists of several packed chromatographic columns connected in series (Figure 1). The SMB technique is based on the simulated counter current flow of fluid and solid phase. This counter current movement is achieved by periodically shifting the inlet and outlet streams in direction of the liquid flow. A feed stream containing a binary mixture to be separated is fed to the process. The less retained component B is carried with the liquid flow and can be collected in the raffinate stream, while the stronger adsorbed component A is carried with the simulated solid flow and can be withdrawn at the extract port.

For the most industrial applications of SMB processes the composition of the fluid phase is constant. This isocratic operation is well established and tools are available to assist layout and optimisation. A lot of work has been done to improve the isocratic

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operation of these continuous chromatographic processes by varying switching times and/or feed concentrations like VariCol (Ludemann et al. (2003)), Powerfeed (Zhang et al. (2003)) or ModiCon (Schramm et al. (2003)). With the introduction of non-isocratic or gradient SMB processes promising attempts for enhanced process performance have been presented recently (Jensen et al. (2000), Abel et al. (2002)).
In these "solvent-gradient" SG-SMB units the inlet streams as there are the fresh eluent and the feed line are fed at different eluent strength to the plant. As consequence a step gradient can be realised with a regime of higher elution strength in sections I and II and one of lower strength of the fluid phase in sections III and IV. Knowing that for instance in section I the desorption of the stronger retained component A has to take place, a higher eluent strength of course is favourable. Similar considerations can be made for section IV where rather low elution strength improves the desired adsorption of the less retained component B.

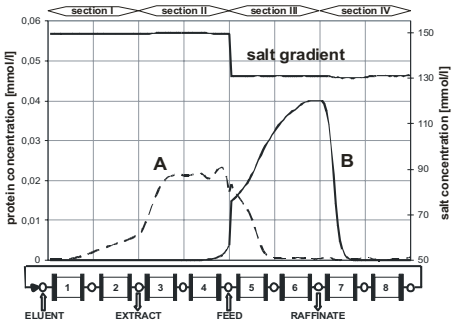

Figure 1. Internal axial concentration profile of a solvent gradient SMB unit (end of switching interval).

The internal axial concentration profiles of the two components to be separated as well as the salt gradient at the end of one switching interval are displayed in Figure 1. These concentration profiles correspond to the experimental operating conditions described in the following parts of this contribution.

2. Theoretical considerations

2.1 Model of the chromatographic column

The transport-dispersive model of a chromatographic column consists of differential mass balances for the fluid and solid phase (Eq. 1 and 2), where non ideal phenomena like axial dispersion and mass transfer limitations are taken into account. For a single column this results in a set of partial differential equations. These are transferred into ordinary differential equations using the Galerkin-Finite-Element method and solved with gPROMS^{TM} as simulation tool. A more detailed description of the model is given by Jupke (2004).

Fluid phase:

$$\frac{\partial c_i}{\partial t} = -u \cdot \frac{\partial c_i}{\partial x} + D_{ax} \cdot \frac{\partial^2 c_i}{\partial x^2} - \frac{3}{r_p} \cdot \frac{(1-\varepsilon)}{\varepsilon} \cdot k_{eff,i} \cdot \left(c_i - c_{p,i} \right) \tag{1}$$

Solid phase:

$$\left(1-\varepsilon_p\right)\cdot\frac{\partial q_i}{\partial t}+k_{d,i}\cdot\varepsilon_p\cdot\frac{\partial c_{pi}}{\partial t}=\frac{3}{r_p}\cdot k_{eff,i}\cdot\left(c_i-c_{p,i}\right) \tag{2}$$

Parameters that result from this model approach are the bed's void fraction ε, the particle porosity ε_p, a size exclusion factor $k_{d,i}$, the axial dispersion D_{ax} and a lumped mass transfer coefficient $k_{eff,i}$. The parameters used for simulation are listed in Table 1.
The model of the SMB process is obtained by interconnecting several single column models (node model) according to the real process set-up considering the dynamic behaviour of the unit.

2.2 Ion exchange equilibrium

The ion exchange equilibrium has been described following the steric mass action (SMA) approach introduced by Brooks et al. (1992). This isotherm model has been developed especially for the ion exchange chromatography of proteins. It considers the sterical hindrance of active sites on the resin by large proteins as well as competitive adsorption behaviour. This model enables a quantitative description of the equilibrium in dependence of the concentration of the influencing counter-ions at constant pH values (Eq. 3 and 4). Beside the total capacity of the ion exchange resin Λ the model requires three parameters for every solute present in the fluid phase. These parameter are the equilibrium constant $K_{s,i}$, the stoichiometric coefficient ν_i as well as the as the steric hindrance parameter σ_i.

$$K_{s,i}=\frac{q_i}{c_i}\cdot\left(\frac{c_s}{q_s}\right)^{\nu_i} \tag{3}$$

$$\Lambda=q_s+\sum\left(\sigma_i+\nu_i\right)\cdot q_i \quad ;i=A,B \tag{4}$$

The relevant parameter can be determined by isocratic pulse as well as break through experiments at different salt concentrations. The isotherm parameters for the separation of β-lactoglobulin A and B are listed in Table 1.

Table 1: Model and isotherm parameter for the given separation problem

ε [-]	0.4		
ε_p [-]	0.57		
Λ [mmol/l]	883		
	chlorid	β-lact A	β-lact B
$K_{S,i}$ [-]	1	$1.45\ 10^{-3}$	$3.5\ 10^{-3}$
σ_i [-]	0	40	40
ν_i [-]	1	6.38	5.14
$k_{eff,i}$ [cm/s]	$0.5\ 10^{-2}$	$0.03\ 10^{-2}$	$0.01\ 10^{-2}$
$k_{d,i}$ [-]	1	0.67	0.67

The presented model with all relevant parameters has been checked for its validity by comparison of single column experiments and the corresponding simulations.

3. Model validation

3.1 Experimental set-up

For all experiments the separation of β-lactoglobulin A and B (Sigma) on the strong anion exchanger Source 30Q (Amersham Biosciences) served as the chromatographic test system. The pH was held constant at a value of 7 buffered with Bis-Tris-Propane while the concentration of the counter ions was adjusted with NaCl.

The SMB experiments were performed on a pilot-scale SMB unit (LICOSEP LAP, Novasep, France) with eight HPLC columns (87 x 10 mm) arranged in a 2-2-2-2 configuration (Figure 1). In this plant one recycle pump and a set of detectors are fix located between column 8 and 1. The set of detectors consists of one conductivity monitor to measure the salt concentration and one UV-detector (280nm) in order to measure the total protein concentration. Since it is not possible to detect the concentration of the single proteins, extra samples have been taken and analysed offline on an analytical HPLC unit to determine the ratio of proteins. To compensate the rather large dead volume produced by the recycle pump and the detectors an asynchronous switching strategy has been applied.

Goal of the separation was to isolate the two proteins at a purity of at least 98%. In order to find suitable operating conditions simulation studies with the complete SMB model have been performed. The chosen operating parameters are listed in Table 2.

Table 2: Operating conditions for the SMB unit and the given separation problem

switching time [min]		25	
async. switching time [min]		7	
feed concentrations [mmol/l]			
	chlorid	β-lact A	β-lact B
feed [-]	116	0.0243	0.0224
eluent[-]	156	0	0
flow rates [ml/min]			
external		internal	
feed	2.17	section I	5.45
eluent	4.04	section II	1.76
extract	3.69	section III	3.93
raffinate	2.52	section IV	1.41

3.2 Results and discussion

The experimental results for the last cycle (switching intervals 17-24) as well as the corresponding simulations are displayed in Figure 2. In part a) the comparison between the measured and calculated salt concentration is given. One can observe the two regimes of different salt concentrations characteristic for the non-isocratic operation of the SMB process.

The second part displays the development of the protein concentration. Beside the measured total concentration the corresponding profile obtained by simulation is shown, while this curve results from the summation of the calculated single protein concentrations. From this diagram it can be seen that during the experiment, especially

at the time of the salt gradient step, total protein concentrations are reached which are almost three times higher than the initial feed concentrations were.
In the last part of Figure 2 the composition of samples taken during the SMB experiment are visualised and compared with the expected composition obtained by simulation.

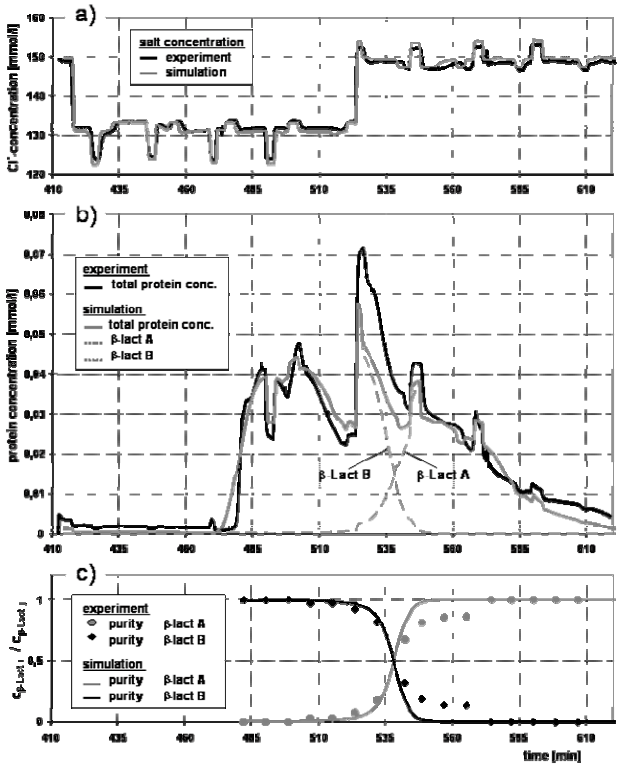

Figure 2 Comparison of the SMB experiment and the corresponding simulation. a) salt concentration; b) protein concentration and c) sample analysis

Figure 2a) shows that the salt concentration temporarily decreases in the first half of the cycle and similarly deviates to higher salt concentrations in the second half. As it can be seen from Figure 2b) these fluctuations in the salt concentrations have a direct impact on the protein concentration. Due to the temporary decrease in salt concentration enhanced adsorption takes place and thus the liquid concentration of the proteins decreases as well. When the concentration of the counter-ions is temporarily increased as it occurs in the second part of the cycle the protein concentration increases too.

4. Model based optimisation

In the foregoing chapter it has been shown that it is possible to describe gradient SMB process with the presented model, since a sufficient agreement between experiment and simulation has been obtained. This means that the model can not be used to find suitable operating parameters only but can also be applied to perform a model based optimisation.

In order to show the potential of the solvent-gradient operation of SMB processes two isocratic processes at constant salt concentrations of 116 mM and 156 mM as well as one gradient SMB (step gradient: 156 – 116 mM) have been optimised to achieve the highest possible productivity. Beside the productivity as main objective function the eluent consumption as well as the relative product concentrations are observed. The reference plant is the one described in chapter 3. The two proteins are isolated at purities higher 99.5%. As a constraint the maximum allowable pressure was taken into account. The results of the optimisations are listed in Table 3.

Table 3: Results of the model based optimisations for different operating conditions

Mode of SMB operation	Productivity	Eluent consumption	Relative product concentrations	
			extract	raffinate
	$[10^{-1}\ g_{Protein}/h]$	$[l_{Eluent}/g_{Product}]$	$[c_{A,ext}/c_{A,feed}]$	$[c_{B,raff}/c_{B,feed}]$
Isocratic (116mM)	1.08	16.7	0.12	1.09
Isocratic (156mM)	2.28	4.6	0.42	1.10
Gradient (156 - 116mM)	7.22	0.4	1.03	2.34

The case studies show that the performance of the gradient operation of the SMB process in terms of productivity, eluent consumption and product concentration is always better than it is for the isocratic modes.

5. Summary

In this contribution a detailed model for the description non-isocratic SMB processes has been introduced. Its ability to describe the real process behaviour has been proven by comparison of experiments and simulation. As presented, this model can be used to assist layout and optimisation of the rather complex SG-SMB processes. As the result of the model based optimisation it has to be pointed out that the non-isocratic operation of SMB processes is able to improve the overall process performance in terms of productivity, eluent consumption and product concentration.

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