A Simulation Tool for Multi Component Chromatography

Bernt Nilsson, Per Borgquist and Patrik Persson

Department of Chemical Engineering I,
Lund Institute of Technology, P.O.Box 124, SE-221 00 Lund, Sweden
email: bernt.nilsson@kat.lth.se   URL: http://www.kat.lth.se

Abstract

Simulation of chromatography processes is time consuming and specially multi component problems. This paper discusses a MATLAB based simulation toolbox for evaluation of multi component chromatographic processes. Experiences from simulation studies are summarised in a set of guidelines for chromatography problems. A set of methods for discretization of chromatography models is compared, including finite difference, finite element and orthogonal collocation. The methods are compared in homogenous and heterogeneous column models and on particle models. Performances of the different batch phases in multi component applications are briefly discussed.

Keywords: Chromatography, Computer tool, Modelling, Numerical methods, Process model, Simulation.

INTRODUCTION

Chromatography is one of the most important separation methods in pharmaceutical and biotechnical industry. It is used both in analytical and preparative applications and it can be based on different chemical and physical mechanisms that creates the separation processes. Ion exchange chromatography uses the charge of the molecules as the separating mechanism, affinity chromatography utilises the affinity of molecules to adsorb on active sites in a stationary carrier and gel filtration separates the molecules due to their diffusive properties in a stationary gel phase. Different chromatography methods are often performed in series creating an important part of the downstream processes in these industries. The different stages should be designed to achieve optimal separation and concentration of the desired components, in our case a protein, from a complex mixture with many different substances.

PREPARATIVE CHROMATOGRAPHY

A preparative chromatography process is often performed in packed bed columns. The packing material is a porous gel, i.e. small beads created by a matrix of a polymer structure. There are other kinds of column configurations, like expanded beds and moving beds, but this work is focused on traditional packed bed columns. A separation is achieved when one or many of the substances in the fluid, the mobile phase, is adsorbed on the packing material, the stationary phase. The separation is complete when the packing material is saturated. Then the column is washed for impurities. Finally the adsorbed substance is eluted. A medium is pumped through the column with properties that makes the proteins to desorb, i.e.

change of pH or ion strength. Before the separation can be restarted the column must be regenerated. This creates a batch-wise process with many important design issues to be considered, like operating conditions for each phase, recovery of product, cycle time, column efficiency, etc. All these parameters have to be considered in order to get optimal conditions. A general reference to preparative chromatography is Sofer and Hagel (1997). A rigorous treatment of the theory behind nonlinear chromatography is found in Guiochon et al. (1994).

CHROMATOGRAPHY MODELS

Chromatographic processes can be described with different types of models which all are dependent in time and space, i.e. nonstationary distributed parameter systems. These are expressed as a set of partial differential equations, PDEs. The different models can be classified as homogeneous or heterogeneous models. Homogenous models describe the adsorption in the column dimension. Heterogeneous models describe it in a microscopic bead dimension, which is coupled with the macroscopic column dimension.

Homogeneous Chromatography Models

All quantities are expressed in the same space dimensions in homogeneous models. One first example is a simple chromatography model based on convection and adsorption. The concentration in the void liquid is modelled as plug flow convection and with an adsorption term as

$$\frac{\partial c}{\partial t} = -\frac{v}{\varepsilon_c}\frac{\partial c}{\partial z} - \frac{1-\varepsilon_c}{\varepsilon_c}\frac{\partial q}{\partial t}$$

and c is the void liquid concentration, t is time and z is the axial column dimension, v is the superficial liquid velocity, ε_c is the column void fraction and q is the concentration of the adsorbed substance. The adsorption can be modelled by a kinetic expression or by an equilibrium isotherm. The adsorption equilibrium is often expressed as a Langmuir isotherm like

$$q = \frac{q_{max}Kc}{1+Kc}$$

where q_{max} is the maximum adsorption capacity and K is the association coefficient. A column model with adsorption equilibrium and convection, often called the Ideal model, becomes a nonlinear first-order PDE in time and in one space dimension. For a detailed discussion of the behaviour of models like this see chap. 6 in Varma and Morbidelli (1997). The second example of a simple model utilises Langmuir kinetics instead of the isotherm. Langmuir kinetics is expressed as

$$\frac{\partial q}{\partial t} = k_{ads}c(q_{max}-q) - k_{des}q$$

where k_{ads} is the adsorption coefficient and k_{des} the desorption coefficient. A column model with convection and Langmuir kinetics consists of two coupled equations and it has a famous analytical solution by Thomas, see for instance Chase (1984).

An extension of the two homogeneous models presented above is to add dispersion in the void liquid as

$$\frac{\partial c}{\partial t} = D_{ax}\frac{\partial^2 c}{\partial z^2} - \frac{v}{\varepsilon_c}\frac{\partial c}{\partial z} - \frac{1-\varepsilon_c}{\varepsilon_c}\frac{\partial q}{\partial t}$$

where D_{ax} is the axial dispersion coefficient. Common boundary conditions, BCs, for this problem are a Robin BC, also called Flux Model, at the inlet and a homogenous von Neumann BC at the outlet.

$$\frac{\partial c}{\partial z} = \frac{v}{D}\left(c - c_{in}\right) \text{ at } z = 0 \; ; \; \frac{\partial c}{\partial z} = 0 \text{ at } z = L$$

Models with equilibrium and dispersion, the Equilibrium-Dispersion models, are frequently reported in the literature, see Guiochon et al. (1994). In adsorption of larger molecules, like proteins, mass transfer becomes important. The models above can be modified with simple lumped mass transfer descriptions. These models add some kind of lumped film resistance to the description above. There are both static and dynamic versions.

Particle Models

As mentioned above mass transfer becomes more important for large molecules and for porous stationary phases. A model of a particle, a porous gel bead, is described with diffusion and adsorption as

$$\frac{\partial p}{\partial t} = D_e\left(\frac{\partial^2 p}{\partial r^2} + \frac{2}{r}\frac{\partial p}{\partial r}\right) - \frac{1}{\varepsilon_p}\frac{\partial q}{\partial t}$$

where p is the pore liquid concentration, r is the radius, D_e is the effective diffusion and ε_p is the bead porosity for the molecule. The last term can be described by a kinetic expression or by an equilibrium expression, similar to the ones discussed above. The model describes the change of the concentration profile in the bead. The boundary condition is a Robin condition at the bead surface ($r = R$).

$$D_e\frac{\partial p}{\partial r} = k(c-p) \text{ at } r = R$$

Here c is the liquid concentration outside the bead. At the origin of the bead the derivative is assumed to be zero (or finite).

Heterogeneous Chromatography Models

Heterogeneous models describe the liquid concentration in void using a column model with dispersion, convection and fluid side mass transfer terms. The diffusion in the particle pores is described together with local adsorption in a particle model. This means that for every position in the macroscopic axial dimension in the column equation there is a corresponding microscopic radial dimension. The pore concentration at the boundary, p_R, is used in the mass transfer term in the coupled column liquid equation

$$\frac{\partial c}{\partial t} = D_{ax}\frac{\partial^2 c}{\partial z^2} - \frac{v}{\varepsilon_c}\frac{\partial c}{\partial z} - \frac{1-\varepsilon_c}{\varepsilon_c}\frac{3}{R}k(c-p_R)$$

and here k is the mass transfer coefficient on the fluid side of the bead. p_R is the pore liquid concentration at the bead surface, i.e. at $r=R$. This example of a heterogeneous model becomes a set of two PDEs in two space dimension and with one local ODE in cases with adsorption kinetics. The model is called heterogeneous as the two space dimensions are described separately. They only interact at a particle and column liquid boundary. This model with kinetics is presented in Carlsson et al. (1994) and with equilibrium in Bautista et al. (1998). A multiple component version of the above model, called VERSE-LC, is reported in Whitley et. al. (1993) and Berninger et al (1991).

CHROMATOGRAPHY SIMULATION

Chromatographic models are expressed as a set of partial differential equations, PDEs. The heterogeneous model with kinetics becomes a set of PDEs. The first is a parabolic-hyperbolic PDE with very strong wave character. The second is a diffusion-adsorption PDE with nonlinear properties. The third equation is the local adsorption equation. These can be solved numerically by the method of lines, MOL, which is the dominating method. Fixed-grid based MOL is reported in Whitley et al (1993), which uses orthogonal collocation on finite elements as discretization into an ODE-system and an implicit DAE-solver, DASSL, see Brenan et al. (1996), for the solution of the ODE-system. Other techniques are reported. These are often based on moving-grid based MOL. The hyperbolic character can be exploited in order to calculate the movement of the grid. Two examples of chromatographic simulations based on this technique are reported in Carlsson et al. (1993) and in Asplund et al. (1997). The use of MATLAB for simulation of different chromatographic models is discussed in Nilsson et al. (1999).

CPS TOOLBOX

The simulation toolbox presented in this paper, called CPS, is based on fixed grid space discretization of the PDEs into a large set of ODEs in time. These are solved by available methods for solutions of ordinary differential equations, ODE-solvers. In chromatography the column axial space dimension is discretized into a large set of grid points due to the strong hyperbolic behaviour. The ODE system is often sparse and stiff, which requires an implicit ODE-solver. The toolbox uses `ode15s` in MATLAB, which is a Gear like solver, and sparse matrix technique for Jacobian calculations, see Champine and Reichelt (1997) for details. Space discretization of the gel beads is often not so critical for the overall simulation performance. The CPS toolbox is a set of MATLAB M-files that facilitate the development of a simulation system of chromatography models and case studies. In CPS toolbox the space derivatives can be discretized with three different method classes, finite difference methods, FDM, finite element methods, FEM, and orthogonal collocation method, OCM.

Example 1: Discretization of a Homogeneous Model

One example of MOL applied on a homogeneous model, with dispersion-convection and Langmuir adsorption kinetic, is the following.

$$\frac{\partial c}{\partial t} = D_{ax}\frac{\partial^2 c}{\partial z^2} - \frac{v}{\varepsilon_c}\frac{\partial c}{\partial z} - \frac{1-\varepsilon_c}{\varepsilon_c}\left(k_{ads}c(q_{max}-q)-k_{des}q\right)$$

$$\frac{\partial q}{\partial t} = k_{ads}c(q_{max}-q)-k_{des}q$$

The general form of the discretized model becomes

$$M\frac{\partial a}{\partial t} = \frac{D_{ax}}{\varepsilon_c}\left(A_2 a + B_2 a_{BC}\right) - \frac{v}{\varepsilon_c}\left(A_1 a + B_1 a_{BC}\right)$$

$$- \frac{1-\varepsilon_c}{\varepsilon_c}\left(k_{ads}q_{max}A_0 a - k_{ads}A_0^m ba - k_{des}A_0^h b\right)$$

$$\frac{\partial b}{\partial t} = k_{ads}q_{max}a - k_{ads}ba - k_{des}b$$

where a is the value (or slope) of the concentration at the grid points in the domain and b is the value of adsorbed substance in the same domain. The discretization matrices, M, A and B, can be calculated with different methods. The a_{BC} is the concentration vector for the fictitious points in FDM or the concentration gradients on the boundaries in FEM. The resulting ODE system can be solved using ODE-solvers in MATLAB. Note that the adsorption equation has no space description and is a local ODE and it does not need any space discretization.

Evaluation of PDE simulation in MATLAB

Before evaluation of the simulation in MATLAB the M-file construction must be optimised. Below follows a number of guidelines that increase the simulation speed independent of the discretization methods.

1. Select an multi-step implicit ODE-solver, i.e. `ode15s`.
2. Create the discretization matrices as sparse.
3. Create the discretization matrices before simulation and declare them as global or in the input argument list.
4. Define the Jacobian. This can be done as an analytical defined Jacobian or as "*jpattern*", a pattern for the nonzero elements in the Jacobian.

Compilation into C-code using MATLAB Compiler 1.2 did not increase the speed, when the compiler could not handle sparse matrices.

FINITE DIFFERENCE METHODS

In FDM the space dimension is discretized into a set of grid points. Space derivatives of a quantity are approximated with a relation between the values of the quantity at the grid points. The relation is found by extensive use of Taylor expansions. The accuracy of the approximation defines the number of grid points and the relation coefficients that are used in the approximation. A second order accurate central-difference approximation of the first and second derivatives looks as follows

$$\frac{\partial c}{\partial z} \approx \frac{c_{i+1}-c_{i-1}}{2h} \;;\; \frac{\partial^2 c}{\partial z^2} \approx \frac{c_{i+1}-2c_i+c_{i-1}}{h^2}$$

In the CPS toolbox there are first, second and fourth order FD-approximations. In column models with

convection FDM needs upwind correction and there is a set of backward difference approximations of first, second and fourth order. A good introduction to FDM is found in Davis (1984) and high order approximations are presented in Schiesser (1991). The boundary conditions can be discretized using fictitious points, see Davis (1984), or by approximations using the domain grid points, see Schiesser (1991).

Example 2: FD-approximation of a Homogeneous Model

Consider a homogeneous model with dispersion, convection and Langmuir kinetics and only four grid points to reduce the complexity, N=4 (2 internal grid points). Central-difference approximation of the dispersion term and backward first order difference approximation of the convection term (upstream correction) give the following matrices

$$A_2 = \frac{1}{h^2}\begin{bmatrix} -2 & 1 & 0 & 0 \\ 1 & -2 & 1 & 0 \\ 0 & 1 & -2 & 1 \\ 0 & 0 & 1 & -2 \end{bmatrix}; B_2 = \frac{1}{h^2}\begin{bmatrix} 1 & 0 \\ 0 & 0 \\ 0 & 0 \\ 0 & 1 \end{bmatrix};$$

$$A_1 = \frac{1}{h}\begin{bmatrix} 1 & 0 & 0 & 0 \\ -1 & 1 & 0 & 0 \\ 0 & -1 & 1 & 0 \\ 0 & 0 & -1 & 1 \end{bmatrix}; B_1 = \frac{1}{h}\begin{bmatrix} -1 & 0 \\ 0 & 0 \\ 0 & 0 \\ 0 & 0 \end{bmatrix}$$

$$M = A_0 = A_0^m = A_0^h = I$$

To solve the problem one also needs the a_{BC}. These are found using the boundary conditions, BCs, for the PDE system. In FDM using the discretization above they are the same as the fictitious points. Common BCs for these problems are a Robin BC, also called Flux Model, at the inlet and a homogenous von Neumann BC at the outlet.

$$\frac{\partial c}{\partial z} = \frac{v}{D_{ax}}(c - c_{in}) \text{ at } z = 0 \text{ and } \frac{\partial c}{\partial z} = 0 \text{ at } z = L$$

A second order accurate central-difference of the BCs becomes as follows

$$\frac{a_1 - a_{-1}}{2h} = \frac{v}{D_{ax}}(a_0 - c_{in}) \text{ at } z = 0;$$

$$\frac{a_{N+1} - a_{N-1}}{2h} = 0 \qquad \text{at } z = L$$

$$a_{BC} = \begin{bmatrix} a_{-1} \\ a_{N+1} \end{bmatrix} = \begin{bmatrix} a_1 - \frac{2hv}{D_{ax}}(a_0 - c_{in}) \\ a_{N-1} \end{bmatrix}$$

The values at the fictitious points are now found and a numerical solution based on the matrices above is possible. Note that the matrices above are problem independent but the BC discretization is problem dependent.

Evaluation of FD-methods

The evaluation of the finite difference methods was based on selection of boundary condition discretization, discretization order and upwind strategy.

1. The method based on fictitious points gives better performance then discretization into the domain. Fictitious points create grid points on the boundary and increase the dimension of the problem but the error becomes smaller.
2. Selection of the order accuracy of the discretization method for the homogenous model is strongly correlated to the upwind strategy. Second order method with upwind performed better then a fourth order method with a poor upwind correction.
3. Best performance gives a five point approximation (fourth order accurate) with one point downwind and three points upwind.

METHOD OF WEIGHTED RESIDUALS

The method of weighted residuals, MWR, is a general framework for describing different discretization procedures. Assume the following integral

$$\int R_i(t,z)W(z) = 0$$

where R is the residual form of the equation and W is the weighting function. Different MWR methods use different residual form and specific weighting functions. In most MWR methods the solution is assumed to be a series of polynomials. This assumed solution is put into the equation creating a residual form. The assumed solution must be differentiable one or two times. In the finite element method the polynomials are assumed to be piecewise define in the domain, (FEM) while in total orthogonal collocation the polynomials are defined in the whole domain (OCM). In the Galerkin method the weighting function is the same as the piecewise polynomial. In collocation methods the weighting function are Dirac delta functions at the collocation points and the MWR integral becomes a series of residual expressions at the collocation points. See Rice and Do (1995) for more details.

FINITE ELEMENT METHODS

In FEM the solution is approximated with a set of finite elements. The elements are piecewise polynomials, the so-called base functions.

$$c(t,z) = \sum a_i(t)p_i(z)$$

The integral results in one equation for each base function, i.e. each element, see Davis (1984). These equations can be expressed in matrix form and the M, A and B matrices are found, see Borgquist (1999) for details.

Example 3: FE-approximation of a Homogeneous Model

Consider a homogeneous model from Example 1 once again and assume four grid points to reduce the complexity, N=4 (3 elements). Discretization matrices or linear base functions becomes as follows

$$A_2 = \frac{1}{h}\begin{bmatrix} 1 & -1 & 0 & 0 \\ -1 & 2 & -1 & 0 \\ 0 & -1 & 2 & -1 \\ 0 & 0 & -1 & 1 \end{bmatrix}; B_2 = \frac{1}{h}\begin{bmatrix} 1 & 0 \\ 0 & 0 \\ 0 & 0 \\ 0 & 1 \end{bmatrix};$$

$$A_1 = \frac{1}{2}\begin{bmatrix} -1 & 1 & 0 & 0 \\ -1 & 0 & 1 & 0 \\ 0 & -1 & 0 & 1 \\ 0 & 0 & -1 & 1 \end{bmatrix}; M = \frac{h}{6}\begin{bmatrix} 2 & 1 & 0 & 0 \\ 1 & 4 & 1 & 0 \\ 0 & 1 & 4 & 1 \\ 0 & 0 & 1 & 2 \end{bmatrix}$$

$$A_0 = A_0^m = M; \qquad A_0^h = I; \qquad B_1 = 0$$

Note that the mass matrix, M, is not a unit matrix and that `ode15s` is used with this mass matrix in order to preserve sparseness. Once again to solve the problem we need the a_{BC}. These are found using the boundary conditions, BCs, for the PDE system. In FEM using the discretization above they are the same as the derivatives on the boundaries.

$$a_{BC} = \begin{bmatrix} -\dfrac{da}{dz}\Big|_{z=0} \\ \dfrac{da}{dz}\Big|_{z=L} \end{bmatrix} = \begin{bmatrix} -\dfrac{v}{D_{ax}}(a_0 - c_{in}) \\ 0 \end{bmatrix}$$

Streamline-Diffusion Stabilisation

In the case of column models dominated by convection the FEM must be modified with some kind of upstream correction. One such method is streamline-diffusion stabilisation, SDS, see Szepessy (1989). In SDS the weighting function is slightly modified so the part of the integral that is upstream is more weighted then the part that is downstream as

$$W_{SDS} = W + k\delta\beta\frac{dW}{dz}$$

where β is equal to the convection coefficient in the homogenous model while $\delta = h - D_{ax}$. Here is h equal to the grid size, see COMSOL (1998). In chromatography applications the SDS gives to much diffusion and the SDS is therefore modified by a

factor, k, which is between 0.3 and 0.5 for best performance in our applications

ORTHOGONAL COLLOCATION METHODS

Parabolic PDEs are successfully solved by the global orthogonal collocation method, see Villadsen and Michelsen (1978), and this method is popular in chemical engineering. The solution of the problem is approximated by a set of orthogonal polynomials. These polynomials are defined in the whole domain, i.e. Lagrange interpolation polynomials. The polynomials are weighted by a coefficient, which is found by the method of weighted residuals, MWR. The weighting functions are Dirac functions at the collocation points and the MWR-integral becomes a set of equations. The collocation points are found as roots to the Jacobi polynomial. These can be expressed in matrix form and the M and A matrices are found. For a good introduction see Rice and Do (1995). Note that OCM uses polynomials that are defined in the whole domain resulting in nonsparse discretization matrices, A, but on the other hand is the mass matrix, M, unity. This means that OCM is not a good method for the column equation. On the other hand OCM is a good method for the particle equation in many cases.

EVALUATION OF METHODS ON CHROMATOGRAPHY MODELS

The methodology and discretization methods discussed above are evaluated on the three major classes of chromatography models.

Homogeneous Models

The column equation is strongly hyperbolic which results in a large number of grid points in the axial dimension. FEM using Galerkin and linear piecewise polynomials together with modified SDS is slightly better then fourth order FDM with upwind modifications, as discussed above. The SDS-FEM is preferred because the stabilisation automatically decreases with grid size and problem parameterisation. Note that the SDS is modified for our applications.

Particle Models

Simulation of the particle equation with adsorption kinetics shows that there are small differences between fourth order FDM, Galerkin-FEM with linear piecewise polynomials and OCM. The reason is that sparseness is not important. OCM is slightly better then the two others for the problems simulated in this study.

Heterogeneous Models

The column equation is strongly hyperbolic as mentioned above, which results in a large number of grid points in the axial dimension. For each grid

point in the axial dimension there is a particle model with one pore diffusion equation and one adsorption equation (in the case of adsorption kinetics). This makes it possible to make hybrid discretization of the problem, using different discretization methods in the axial column and in the particle domain. The best method in our applications is fourth order accurate FDM in the axial dimension and OCM in the particle domain.

Problem Size

Assume that the axial column dimension has N_{ax} grid points and the radial particle dimension is discretized with N_p grid points. All these equations are defined for each chemical component. Assume that the number of components is N_{comp}. This means that the size of a multi component heterogeneous simulation problem becomes

$$N_{tot} = N_{comp} \, N_{ax} \, (1 + 2 \, N_p)$$

Note that the coefficient 2 is the adsorption kinetics. Experience has shown that the number of grid points in the particle must be between 5%-10% of the column grid points in order to give error in the same order of magnitude as the column discretization. This rule of thumb change with the isotherm parameters. Note that this recommendation is valid for heterogeneous models with adsorption kinetics. For heterogeneous models with only diffusion the recommendation is only 2%-3%. This guideline means that we can use the number of column grid points as a price/performance parameter.

Example 4: Intraparticle behaviour

The dynamic response of a heterogeneous model with Langmuir kinetics is shown in Figure 1. The problem is solved with a hybrid discretization method using 50 internal grid points in the column and 5 internal points in the particles for two components, in total ca.
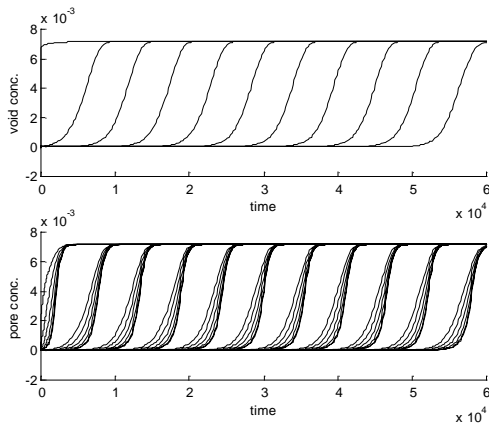

Figure 1: Dynamic responses of 10 grid points in the column liquid with corresponding particle grid points.

1320 states. In the upper plot in Figure 1 the responses of 10 (of 51) column grid points are shown. The lower plot shows the responses of the corresponding 10 pore liquid concentrations in the particle. The column equation is discretized with a fourth order FDM with upwind correction. The particles are discretized by Galerkin-FEM.

BATCH CYCLE SIMULATION

The CPS toolbox can be used to simulated batch cycles including four main batch phases, namely adsorption, wash, elution and regeneration.

Adsorption

In this batch phase the process medium is pumped into the column. It is desired to create as steep concentration profile as possible. This means that the whole column capacity is used for adsorption. This phase is aborted when the output concentration is over a certain value, e.g. 5% of the inlet concentration. If the separated protein is expensive this may be lower or if it is not it can be higher. Interesting performance indices are the amount of losses, W_{ads}, and used column capacity, Q_{ads}.

$$W_{ads} = \frac{\int_0^{t_b} w c_{out} dt}{w c_{in} t_b} \; ; \; Q_{ads} = \frac{\iiint_{V_{gel}} q \, dV_{gel}}{q_{eq} V_{gel}}$$

w is the volumetric flow rate, c is the concentrations, t_b is the break time, q is the adsorbed concentration, q_{eq} is the equilibrium concentration for the inlet concentration and V_{gel} is the gel volume.

Example 5: Adsorption Performance

The simulation of the adsorption batch phase, seen in Figure 1, has the following performance indices for two different flow rates listed in Table 1, below.

Table 1: Evaluation indices for two different flows at two different break concentrations.

flow rate	break % (s)	W_{ads}	Q_{ads}
1.67e-8	0.05 (52596)	0.0015	0.93
1.67e-8	0.10 (53427)	0.0027	0.94
2.50e-8	0.05 (34248)	0.0021	0.91
2.50e-8	0.10 (35033)	0.0038	0.93

We see in Table 1 that protein losses increase with increase flow and in this case the flow rate is increased by 50%. On the other hand the break time is decreased, which makes it possible to increase the productivity.

Wash

Impurities that do not adsorb are washed out from the column by pumping clean buffer. In this phase we would like to wash out as much impurities as possible but on the other hand minimise loss of goal protein and buffer medium. This phase is aborted when the

impurities are below a certain value or just when a given volume of buffer is consumed.

Example 6: Wash Simulation

A simulation of the wash phase is seen in Figure 2. The initial values are the values when the adsorption is aborted at 5% and the wash phase uses the same flow rate. Washing volume is only 1.3 times the column volume and the loss index is 0.045.
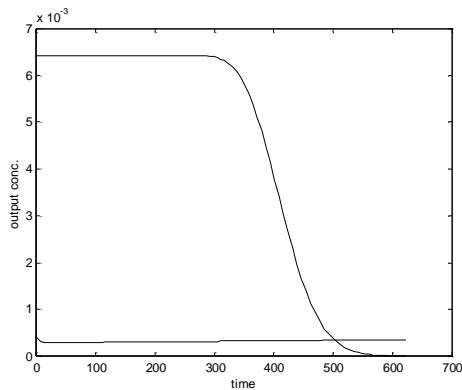

Figure 2: Output concentrations for impurities (upper curve) and proteins (lower curve) during wash.

Elution

When the column is washed the adsorbed components are eluted out from the column. This can be done in a number of different ways. They can be displaced by a displacement component, a chemical component that adsorbs harder to the stationary phase. This means that it push other components out in the liquid and out from the column. They can also be eluted by a different elution media, which changes the chemical properties in the column, causing the components to desorb. The adsorbed components leave the column in elution peaks. There is a trade-off between concentration of the final sample and loss of protein.

Example 7: Elution

The elution profiles are seen in Figure 3. The initial values are the values when the wash phase is aborted. The recovery in elution phase is approximately 86% of the injected protein and with a concentration increase of 12 times. The impurities are almost totally removed.

Regeneration

Regeneration is similar to washing. Buffer is pumped through the column to reset the chemical properties after elution. On the same time it is important to minimise the loss of buffer.

MULTI COMPONENT APPLICATION

A simple three component application is breifly presented. The components are three proteins that
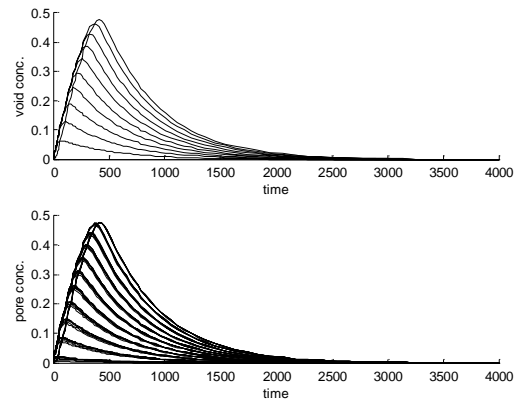

Figure 3: Elution profiles of 10 grid points (of 50) in the column liquid (upper plot) and in the corresponding pore liquid grid points.

have almost the same physical characters. They are assumed to be of almost the same size. Their chemical properties are different and they have different adsorption isoterms. The component A is our goal protein. Component B is assumed to adsorbe 100 times weaker to the stationary phase, while component C is adsorbed 2 times harder. This means that the component will pass the column in the order B, A and C. The adsorption is aborted when component A reaches 5% at the outlet. This means that component B has been measured at the outlet for a long time and component C can not be measured, as seen in Figure 4.
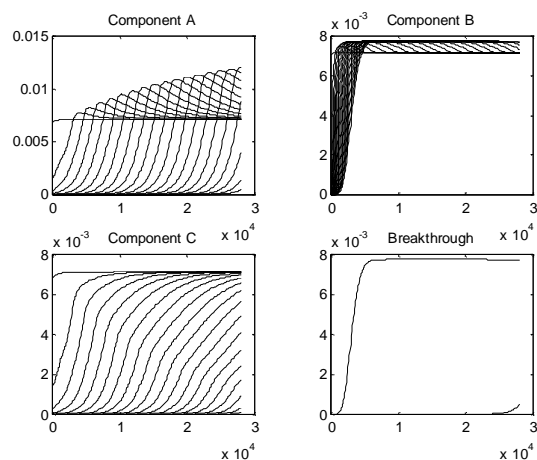

Figure 4: Three component adsorption responces of 20 grid points in the column liquid.

The washing phase is done by using a washing volume of 4 column volumes. It is clearly seen that the weak adsorbed component B is almost washed out from the column is this step. The responses of 20 grid points is seen in Figure 5.

In this application Langmuir kinetics is used to model the adsorption. This means that the adsorption model can not handle elution directly and the Langmuir coefficients must be adjusted for the elution phase. In this xample it is assumed that both component A
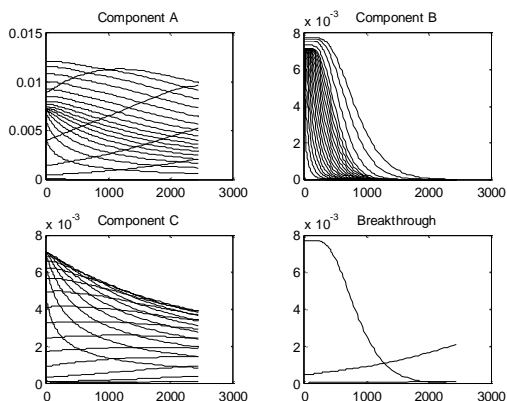
Figure 5: *Wash of the three components. Note that component B is almost totally wash out.*

and B will elute for the selected elution medium. Component C do not elute for the selected medium. The result is that component A will elute together with small amount of component C. Component B has almost totally been wash out in the previous step. This is clearly seen in Figure 6. The resulting chromatogram is shown in Figure 7.

CONCLUSIONS

This paper has presented a toolbox in MATLAB for simulation of multi component chromatographic processes. The CPS toolbox facilitates the development of simulations based on the state-of-the art in numerical solution technique. Experiences from simulations are summarised in a set of guidelines for chromatography problems. Simulations of chromatography models, particular models that are heterogeneous, require large computer resources (today). In order to decrease the burden the MATLAB code can be optimised in a number ways. This is often more important then selection of discretization method. It is shown that the toolbox is well suited for simulation and evaluation of whole batch cycle studies.
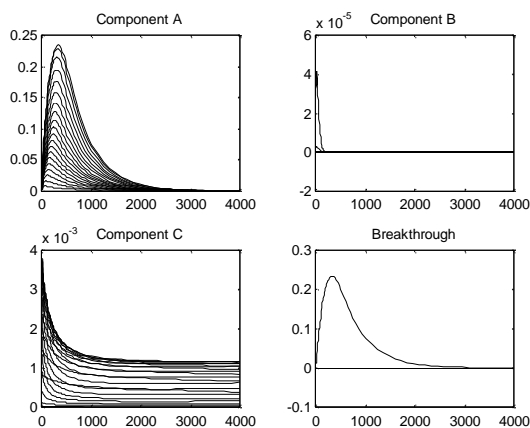

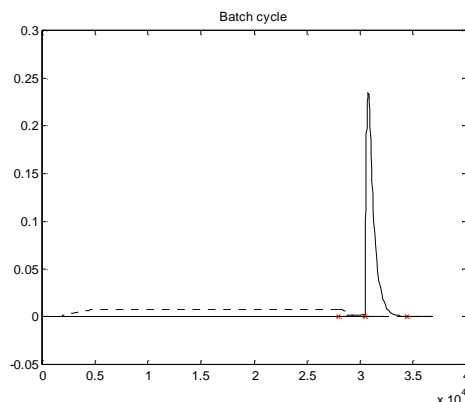**Figure 6**: *Elustion phase where component A is eluted.*

Figure 7: *The resulting chromatogram for the three component application.*

REFERENCES
Asplund, S.E and, Edvinsson, R.E., (1997), "A Method for the Rapid Simulation of Preparative Liquid Chromatography" *Computers Chem.Engng.*,

Borgquist, P-O, (1999), *Simulering av kromatografiprocesser*, (Simulation of Chromatographic Processes, in swedish) LUTKDH/(TKKA-5005)/1-90/(1999), Dept. of Chemical Engineering 1, Lund Institute of Technology, Lund, Sweden.

Bautista, L.F., Martinez, M., and Aracil, J., (1998), "Phenomenological Modelling of Chromatographic Processes in Biotechnology", In *Proc. of SPICA 98*, Tondeur (ed).

Berninger, J.A., R.D. Whitley, X. Zhang and N.-H. L. Wang, (1991), "A Versatile Model for Simulation of Reaction and Nonequilibrium Dynamics in Multicomponent Fixed-bed Adsorption Processes", *Computers Chem.Engng.*, Vol 15, No. 11, pp.749-768.

Brenan, K.E., Campbell, S.L. and Petzold, L.R. (1996), *Numerical Solution of Initial-Value Problems in Differential-Algebraic Equations*, SIAM.

Carlsson, F., Axelsson, A., Zacchi, G., (1994), "Mathematical modelling and parametric studies of affinity chromatography", *Computers Chem.Engng.*, Vol 18, Suppl, p.657-661.

Chase, H.A., (1984), "Prediction of the Performance of Preparative Affinity Chromatography", *J. of Chrom.*, 297, pp 179-202.

COMSOL, (1998), *FEMLAB- Reference Manual*, COMSOL AB, Stockholm, Sweden.

Davis, M.E, (1984), *Numerical Methods and Modeling for Chemical Engineers*, chap 2-4.

Guiochon, G., Shirazi, S.G. and Katti, A.M., (1994), *Fundamentals of Preparative and Nonlinear Chromatography*, Academic Press.

Nilsson, B., Borgquist, P.O., Axelsson, A., Zacchi, G., (1999), "Simulation of Chromatographic Processes using MATLAB", *Computers Chem.Engng.*, Vol 23, Suppl, p.S715-S718.

Rice, R.G. and Do, D.D., (1995), *Applied Mathematics and Modeling for Chemical Engineers*, Wiley, chap. 8 and 12.

Schiesser, W.E., (1991), *The Numerical Method of Lines*, Academic Press.

Shampine, L.F., and Reichelt, M.W., (1997), "The MATLAB ODE Suite", *SIAM J. Sci. Comput.*, Vol. 18, No. 1, pp. 1-22.

Sofer, G., and Hagel, L., (1997), *Handbook of Process Chromatography*, Academic Press.

Szepessy, A., (1989), "Convergence of the Streamline Diffusion Finite Element Method for Conservation Laws", *PhD thesis*, Dept. of Mathematics., Chalmers Institute of Technology, Göteborg, Sweden.

Varma, A., and Morbidelli, M., (1997), *Mathematical Methods in Chemical Engineering*, Oxford University Press, chap 6.

Villadsen, J., and Michelsen, M.L., (1978*), Solution of Differential Equation Models by Polynomial Approximation*, Prentice-Hall.

Whitley, R.D., K.E. Van Cott and N.-H. L. Wang, (1993), "Analysis of Nonequilibrium Adsorption/Desorption Kinetics and Implications for Analytical and Preparative Chromatography", *Ind.Eng.Chem.Res.*, *32*, pp.149-159.