Modeling of Nonlinear Multicomponent Chromatography

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Advances in Biochemical Engineering
Biotechnology, Vol. 49
Managing Editor: A. Fiechter

In the age of rapid development of biotechnology, preparative and large scale chromatography becomes more and more popular. Unlike analytical chromatography, dispersion and mass transfer effects are often significant in preparative and large scale chromatography. Concentration overload often leads to nonlinearity of the system. The study of nonlinear chromatography becomes more and more demanding. Much work has been done in the past two decades, but many topics of practical importance still need to be tackled. In this chapter, a review is given on different models for chromatography. This chapter provides a brief review of different mathematical models for nonlinear chromatography. A general multicomponent rate model, which accounts for various mass transfer mechanisms and nonlinear isotherms is presented. This comprehensive model is a very powerful tool for the study of the dynamics of nonlinear multicomponent chromatography. This chapter also presents an efficient numerical method for the solution of the model and its numerous extensions. As an example, the model is used for the study of some interesting effects of isotherm characteristics of the displacer on the optimization of stepwise displacement.

List of Symbols

Symbol	Description
a_i	constant in Langmuir isotherm for component i, $b_i C_i^{\infty}$
b_i	adsorption equilibrium constant for component i, k_{ai}/k_{di}
Bi_i	Biot number of mass transfer for component i, $k_i R_p/(\varepsilon_p D_{pi})$ or $k_i R_p/(\varepsilon_{pi}^a D_{pi})$
C_{bi}	bulk phase concentration of component i
C_{fi}	feed concentration profile of component i, a time dependent variable
C_{0i}	concentration used for nondimensionalization, $\max\{C_{fi}(t)\}$
C_{pi}	concentration of component i in the stagnant fluid phase inside particle macropores
C_{pi}^s	concentration of component i in the solid phase of particle (mole adsorbate/unit volume of particle skeleton)
C_i^{∞}	adsorption saturation capacity for component i (mole adsorbate/unit volume of particle skeleton)
$\bar{C}$	adsorption saturation capacity based on the unit volume of the bed
$\bar{C}_i$	concentration of component i in the stationary phase based on the unit volume of the bed
C_i	concentration of component i in the fluid phase based on the unit volume of the bed
c_{bi}	$= C_{bi}/C_{0i}$
c_{pi}	$= C_{pi}/C_{0i}$
c_{pi}^s	$= C_{pi}^s/C_{0i}$
c_i^{∞}	$= C_i^{\infty}/C_{0i}$
D_{bi}	axial or radial dispersion coefficient of component i
Da_i^a	Damköhler number for adsorption, $\dfrac{L(k_{ai}C_{0i})}{v}$
Da_i^d	Damköhler number for desorption, Lk_{di}/v
F_i^{ex}	size exclusion factor for component i, $\varepsilon_{pi}^a/\varepsilon_p$

k_i	film mass transfer coefficient of component i
k_{ai}	adsorption rate constant for component i
k_{di}	desorption rate constant for component i
L	column length
N	number of interior collocation points
Ne	number of quadratic elements
Ns	number of components
Pe_{Li}	Peclet number of axial dispersion for component i, vL/D_{bi}
R	radial coordinate for particle
R_p	particle radius
r	$= R/R_p$
t	time
v	interstitial velocity
Z	axial coordinate
z	$= Z/L$

Greek Letters

ε_b	bed void volume fraction
ε_p	particle porosity
ε_{pi}^a	accessible particle porosity of component i
η_i	dimensionless constant, $\dfrac{\varepsilon_p D_{pi} L}{R_p^2 v}$
ξ_i	dimensionless constant for component i, $3Bi_i\eta_i(1-\varepsilon_b)/\varepsilon_b$
τ	dimensionless time, $\dfrac{vt}{L}$
τ_{imp}	dimensionless time duration for a rectangular pulse of the sample
ϕ	Lagrangian interpolation function

1 Review of Models for Chromatography

A very comprehensive review on the dynamics and mathematical modeling of adsorption and chromatography was given by Ruthven [1]. Models in this area are generally classified into three categories [1]: equilibrium theory, plate models and rate models.

1.1 Equilibrium Theory

Glueckauf [2] is considered as being the first person to develop the equilibrium theory of multicomponent isothermal adsorption [1]. The theory further developed into the interference theory by Helfferich and Klein [3] is mainly aimed at stoichiometric ion-exchange systems with constant separation factors. A mathematically parallel treatise for systems with multicomponent Langmuir isotherms was developed by Rhee and co-workers [4, 5].

Equilibrium theory assumes direct local equilibrium between the mobile phase and the stationary phase, neglecting axial dispersion and mass transfer resistances. The theory gives good interpretation of experimental results for chromatographic columns with fast mass transfer rates shown by many analytical and some preparative columns. It can provide general location of the concentration profiles of a chromatographic system but fails to provide accurate details if mass transfer effects in the system are significant [6]. Equilibrium theory has been widely used for the study of multicomponent interference effects [3] and ideal displacement development [5]. Many cases of practical application have been reported [3, 7–12].

1.2 Plate Models

Generally speaking, there are two kinds of plate models, which may also be called staged models or staged theories [13]. The first kind is directly analogous to the "tanks in series" model for nonideal flow systems [1]. In such a model, the column is divided into a series of small artificial elements. Inside each element the content is assumed to be completely mixed. This gives a set of first order ordinary differential equations (ODE's) that describe the adsorption and interfacial mass transfer processes. Many researchers have contributed to this kind of plate model [1, 14–16]. However, plate models of this kind generally are not suitable for multicomponent chromatography since the equilibrium stages may not be assumed equal for different components.

The other kind of plate model is formulated based on the distribution factors which determine the equilibrium of each component in each of the artificial stages, and the model solution involves recursive iterations, rather than solving for ODE systems. The most popular of this kind are the Craig distribution models. Considering the blockage effect, the Craig models are applicable to

multicomponent systems. Descriptions of Craig models were given by Eble et al. [17], Seshadri and Deming [18], and Solms et al. [19]. In recent years, Craig models have been extensively used for the study of column overload problems [17, 20].

1.3 Rate Models

The word "rate" refers to the rate expression or rate equation for the mass transfer between the mobile phase and the stationary phase. A rate model usually consists of two sets of differential mass balance equations, one for the bulk-fluid phase, the other for the particle phase. Different rate models have different complexities. A comprehensive review of rate models was given by Ruthven [1].

1.3.1 Rate Expressions and Particle Phase Governing Equations

The solid film resistance hypothesis was first proposed by Glueckauf and Coates [21]. It assumes a linear driving force between the equilibrium concentrations in the stationary phase (determined from the isotherm) and the average fictitious concentrations in the stationary phase. Because of its simplicity, this rate expression has been used by many researchers [1, 22–25] but this model cannot provide the details of the mass transfer processes.

The fluid film resistance mechanism which also assumes a linear driving force is widely used [1]. It is often called external mass transfer resistance. If the concentration gradient inside the particle phase is ignored, the model then becomes the lumped particle model, which has been used by some researchers [27–29]. If the Biot number for mass transfer, which reflects the ratio of the characteristic rate of film mass transfer over that of intraparticle diffusion, is much larger than 1, the external film mass transfer resistance can be neglected with respect to pore diffusion.

In many cases both external mass transfer and intraparticle diffusion must be considered. A local equilibrium is often assumed between the concentration in the stagnant fluid phase inside macropores and the solid phase of the particle. Such a rate mechanism is adequate to describe the adsorption and mass transfer between the bulk-fluid phase and the particle phase, and inside the particle phase in most chromatographic processes. The local equilibrium assumption here is different from that made for the equilibrium model which assumes a direct equilibrium of concentrations in the solid and the liquid phase without any kind of mass transfer resistances.

1.3.2 Adsorption Kinetics and Affinity Chromatography

In some cases, the adsorption and desorption rates may not be high enough and the assumption of the local equilibrium between the concentration in the

stagnant fluid phase inside macropores and the solid phase of the particle is no longer valid. Kinetic models must be used. Some kinetic models were reviewed by Ruthven [1] and Lee et al. [30]. The second order kinetics has been widely used in affinity chromatography [31–39]. If the saturation capacities for all the solutes are the same, the second order kinetics reduces to the Langmuir isotherm when equilibrium is assumed.

1.3.3 Governing Equations for Bulk-Fluid Phase

The partial differential equation for the bulk-fluid phase can be easily obtained with differential mass balances. They usually contain the following terms: axial dispersion, convection, transient, and the interfacial flux. Such equations themselves are generally linear if physical parameters are not concentration dependent. They become nonlinear when coupled with nonlinear rate expressions.

Analytical solutions may be obtained using Laplace transformation [39, 40] for many isothermal, single component systems with linear isotherms. The linear operator method [41] can also be used to solve problems in linear chromatography. For more complex systems, especially those involving nonlinear isotherms, analytical solutions generally cannot be derived [1]. With the rapid growth of the availability of fast and powerful computers and development of efficient numerical methods, it is now possible to obtain numerical solutions to complex rate models that consider various forms of mass transfer mechanisms [42]. Complex rate models are now becoming more and more popular especially in the study of preparative and large scale chromatography.

1.4 General Multicomponent Rate Models

A rate model which considers axial dispersion, external mass transfer, intraparticle diffusion and nonlinear isotherms is considered a general multicomponent rate model. Such a general model is adequate in most cases to describe the adsorption and mass transfer processes in multicomponent chromatography. In some cases surface adsorption and size exclusion, adsorption kinetics, etc., may have to be included to give an adequate account for a particular system.

Several groups of researchers have proposed and solved various general multicomponent rate models using different numerical approaches [42–45].

1.5 Solution to the General Multicomponent Rate Models

A general multicomponent rate model consists of a coupled PDE system with two sets of mass balance equations in the bulk-fluid and particle phases for each component, respectively. The transient PDE system becomes nonlinear if any nonlinear isotherms or nonlinear kinetics are involved in the system.

The finite difference method is a very simple numerical procedure and can be directly applied for the solution to the model [45, 46], but this procedure often requires a huge amount of memory space, and its efficiency and accuracy are not competitive compared with other advanced numerical methods, such as orthogonal collocation (OC), finite element, and orthogonal collocation on finite element (OCFE).

The general strategy for solving a nonlinear transient PDE system numerically using the advanced numerical methods is to discretize the spatial axes in the model equations first, and then solve the resulting ODE system using an ODE solver.

1.5.1 Discretization of Particle Phase Equations

The OC method is a very accurate, efficient and simple method for discretization. It has been widely used for particle problems [47, 48] and is obviously the best choice for the particle phase governing equations of general multicomponent rate models [42, 43, 44].

1.5.2 Discretization of Bulk-Fluid Phase Equations

Concentration gradients in the bulk-fluid phase can be very stiff, thus, the OC method is no longer suitable, since global splines using high order polynomials are very expensive [48] and sometimes not stable. The OCFE method uses linear elements for global spline and collocation points inside each element. No numerical integration for element matrices is needed because of the use of linear elements. This discretization method can be used for systems with stiff gradients [48].

The finite element method with a higher order of interpolation functions (typically quadratic, or occasionally cubic) is a very powerful method for stiff systems. Its highly streamlined structure provides unsurpassed convenience and versatility. This method is especially useful for systems with variable physical parameters, such as radial flow chromatography and nonisothermal adsorption with or without chemical reaction. Chromatography of some biopolymers also involves variable axial dispersion coefficient [49].

1.5.3 Solution to the ODE System

If the finite element method is used for the discretization of bulk-fluid phase equations and OC for the particle phase equations, an ODE system then results. The ODE system with initial values can be readily solved using an ODE solver such as subroutine IVPAG of the IMSL [50], which uses the powerful Gear's stiff method [51].

If the discretization of the bulk-fluid phase equations is carried out using the OCFE method, an ODE system coupled with some algebraic equations which come from the continuity of boundary fluxes results [44, 48]. The system can be solved using an available differential algebraic equation solver.

Such a system can also be conveniently solved with an ODE solver if one manipulates the user-supplied function subroutine which evaluates the concentration derivatives for the ODE solver to eliminate those algebraic equations in an in situ fashion. This is possible since the trial concentrations are given as arguments for the subroutine. This approach helps reduce the total number of equations in the final system. It was apparently adopted by Gardini et al. [52], for a multi-phase reaction engineering problem.

2 A General Multicomponent Rate Model for Axial Flow Chromatography

2.1 Model Assumptions

Figure 1 shows the anatomy of a chromatographic column with axial flow. The following basic assumptions are needed for the formulation of the general rate model.

- The multicomponent fixed-bed process is isothermal.
- The bed is packed with porous adsorbents which are spherical and uniform in size.
- The concentration gradients in the radial direction of the bed are negligible.
- Local equilibrium exists for each component between the pore surface and the stagnant fluid phase in the macropores.
- The diffusional and mass transfer coefficients are constant and independent of the mixing effects of the components.

2.2 Model Formulation

Based on these basic assumptions, the following governing equations can be formulated from the differential mass balances for each component in the bulk-fluid and the particle phases.

$$-D_{bi}\frac{\partial^2 C_{bi}}{\partial Z^2}+v\frac{\partial C_{bi}}{\partial Z}+\frac{\partial C_{bi}}{\partial t}+\frac{3k_i(1-\varepsilon_b)}{\varepsilon_b R_p}(C_{bi}-C_{pi,R=R_p})=0 \qquad (1)$$

$$(1-\varepsilon_p)\frac{\partial C^s_{pi}}{\partial t}+\varepsilon_p\frac{\partial C_{pi}}{\partial t}-\varepsilon_p D_{pi}\left[\frac{1}{R^2}\frac{\partial}{\partial R}\left(R^2\frac{\partial C_{pi}}{\partial R}\right)\right]=0 \qquad (2)$$

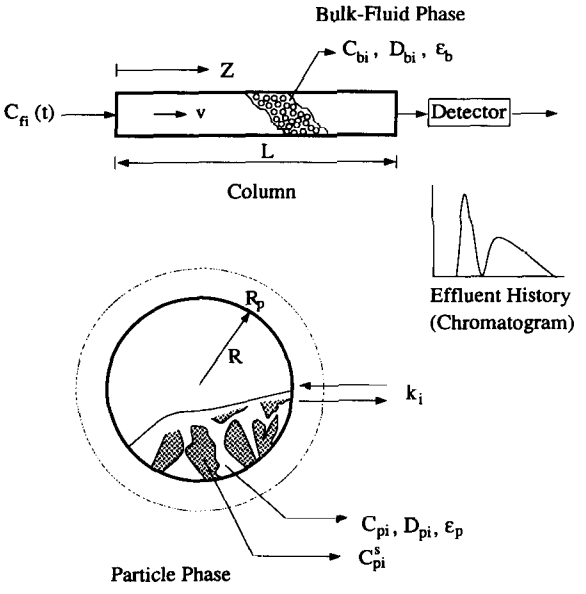

Fig. 1. Anatomy of a chromatographic column

with the initial and boundary conditions

$$t = 0, \quad C_{bi} = C_{bi}(0,Z),\ C_{pi} = C_{pi}(0,R,Z) \tag{3, 4}$$

$$Z = 0, \quad \frac{\partial C_{bi}}{\partial Z} = \frac{v}{D_{bi}}(C_{bi} - C_{fi}(t)) \quad Z = L, \quad \frac{\partial C_{bi}}{\partial Z} = 0 \tag{5, 6}$$

$$R = 0, \quad \frac{\partial C_{pi}}{\partial R} = 0 \qquad R = R_p, \quad \frac{\partial C_{pi}}{\partial R} = \frac{k_i}{\varepsilon_p D_{pi}}(C_{bi} - C_{pi,R=R_p}) \tag{7, 8}$$

Equations (1) and (2) are coupled via C_{pi}, $R = R_p$ which is the concentration of component i at the surface of a particle. In Eq. (2), C^s_{pi} is the concentration of component i in the solid phase of the adsorbents based on the unit volume of the solid, excluding pores. It is directly linked to the multicomponent isotherms which couple the PDE system based on assumption (4). Concentrations C_{bi} and C_{pi} are based on the unit volume of mobile phase fluid. The effective diffusivities, D_{pi}, in this work do not include the particle porosity.

By introducing the following dimensionless terms

$$c_{bi} = C_{bi}/C_{0i},\ c_{pi} = C_{pi}/C_{0i},\ c^s_{pi} = C^s_{pi}/C_{0i},\ r = R/R_p,\ z = Z/L,\ \tau = vt/L$$

$$Pe_{LI} = vL/D_{bi},\ Bi_i = k_i R_p/\varepsilon_p D_{pi},\ \eta_i = \varepsilon_p D_{pi} L/R_p^2 v,\ \xi_i = 3Bi_i \eta_i (1 - \varepsilon_b)/\varepsilon_b$$

the PDE system can be transformed into the following dimensionless forms.

$$-\frac{1}{Pe_{Li}}\frac{\partial^2 c_{bi}}{\partial z^2}+\frac{\partial c_{bi}}{\partial z}+\frac{\partial c_{bi}}{\partial \tau}+\xi_i(c_{bi}-c_{pi,r=1})=0 \tag{9}$$

$$\frac{\partial}{\partial \tau}[(1-\varepsilon_p)c_{pi}^s+\varepsilon_p c_{pi}]-\eta_i\left[\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial c_{pi}}{\partial r}\right)\right]=0 \tag{10}$$

I. C.

$$\tau=0, \qquad c_{bi}=c_{bi}(0,z), \quad c_{pi}=c_{pi}(0,r,z) \tag{11, 12}$$

B. C.

$$z=0, \qquad \frac{\partial c_{bi}}{\partial z}=Pe_{Li}(c_{bi}-C_{fi}(\tau)/C_{0i}) \tag{13}$$

For frontal adsorption $C_{fi}(\tau)/C_{0i}=1$

For elution $C_{fi}(\tau)/C_{0i}=\begin{cases}1 & 0\le\tau\le\tau_{imp}\\ 0 & \text{else}\end{cases}$

After the sample introduction (in the form of frontal adsorption):

if component i is displaced, $C_{fi}(\tau)/C_{0i}=0$

if component i is a displacer, $C_{fi}(\tau)/C_{0i}=1$

$$z=1, \qquad \frac{\partial c_{bi}}{\partial z}=0 \tag{14}$$

$$r=0, \qquad \frac{\partial c_{pi}}{\partial r}=0 \qquad r=1, \quad \frac{\partial c_{pi}}{\partial r}=Bi_i(c_{bi}-c_{pi,r=1}) \tag{15, 16}$$

Note that all the dimensionless concentrations are based on C_{0i} which is equal to the maximum of the feed profile $C_{fi}(\tau)$. For example, in an elution, if component i is a sample solute in the sample which is injected as a rectangular pulse, the profile of $C_{fi}(\tau)$ is then of a rectangular shape, and its upper boundary value is the value of C_{0i}.

3 Numerical Solution to the Model

An efficient and robust numerical procedure has been developed by Gu et al. [42] for the solution to the above PDE system. It involves two parts. First, the spatial axes, z and r, are discretized. And then the resulting ODE system (with initial values) is solved with an ODE solver (integrator). An overview of the general strategy for the solution is shown in Figure 2.

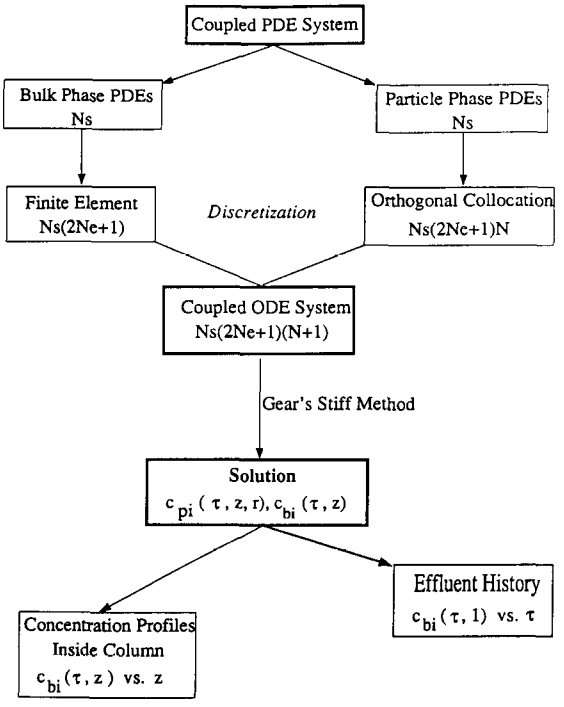

Fig. 2. Solution strategy for the general multicomponent rate model

3.1 Discretization

Equations (9) and (10) can be discretized into a set of ODE's by the finite element and the OC methods respectively. Using the Galerkin approximation and the first weak form [53], Eq. (9) becomes

$$[\mathbf{DB}_i][\mathbf{c}'_{bi}] + [\mathbf{AKB}_i][\mathbf{c}_{bi}] = [\mathbf{PB}_i] + [\mathbf{AFB}_i] \tag{17}$$

where

$$(\mathbf{DB}_i)^e_{m,n} = \int \phi_m \phi_n \, dz \tag{18}$$

$$(\mathbf{AKB}_i)^e_{m,n} = \int \left(\frac{1}{Pe_{Li}} \frac{\partial \phi_m}{\partial z} \frac{\partial \phi_n}{\partial z} + \phi_m \frac{\partial \phi_n}{\partial z} + \xi_i \phi_m \phi_n \right) dz \tag{19}$$

$$(\mathbf{AFB}_i)^e_m = \int \xi_i \phi_m c_{pi,r=1} \, dz \tag{20}$$

in which m, $n \in \{1, 2, 3\}$, and the superscript e indicates that the finite element matrices and vectors are evaluated over each individual element before global assembly. Four point Gauss-Legendre quadratures [53] are used for integrations. The superscript prime in this work indicates a first order time derivative. The bold face variables indicate matrices or vectors. The natural boundary

condition $(\mathbf{PB}_i)|_{z=0} = -c_{bi} + C_{fi}(\tau)/C_{0i}$ will be applied to $[\mathbf{AKB}_i]$ and $[\mathbf{AFB}_i]$ at $z = 0$. $(\mathbf{PB}_i) = 0$ anywhere else.

Using the same symmetric polynomials as defined by Finlayson [48], Eq. (10) is transformed to the following equation by the OC method.

$$\left(\sum_{j=1}^{Ns} \frac{\partial g_i}{\partial c_{pj}} \frac{dc_{pj}}{d\tau} \right)_1 = \eta_i \sum_{k=1}^{N+1} \mathbf{B}_{1,k}(c_{pi})_k, \quad 1 = 1, 2, \ldots, N \tag{21}$$

in which $g_i = (1 - \varepsilon_p)c_{pi}^s + \varepsilon_p c_{pi}$. Note that g_i for each component i contains the nonlinear multicomponent isotherms. The value of $(c_{pi})_{N+1}$ (i.e., $c_{pi,r=1}$) can be obtained from the boundary condition at $r = 1$, which gives

$$\sum_{j=1}^{N+1} \mathbf{A}_{N+1,j}(c_{pi})_j = \mathbf{Bi}_i(c_{bi} - c_{pi,r=1}) \tag{22}$$

or

$$c_{pi,r=1} = \frac{\mathbf{Bi}_i c_{bi} - \sum_{j=1}^{N} \mathbf{A}_{N+1,j}(c_{pi})_j}{\mathbf{A}_{N+1,N+1} + \mathbf{Bi}_i} \tag{23}$$

where the matrices **A** and **B** are the same as defined by Finlayson [48].

3.2 Solution to the ODE System

If Ne quadratic elements (i.e. (2Ne + 1) nodes) are used for the z-axis in bulk-fluid phase equations and N interior OC points are used for the r-axis in particle phase equations, the above discretization procedure gives Ns (2Ne + 1) (N + 1) ODE's which are then solved simultaneously by Gear's stiff method [50]. A function subroutine must be supplied to the ODE solver to evaluate concentration derivatives at each element node and OC point with given trial concentration values. The concentration derivatives at each element node (c'_{bi}) are easily determined from Eq. (17). The concentration derivatives at each OC point (c'_{pi}) are coupled because of the complexity of the isotherms which are related to g_i via c_{pi}^s. At each interior OC point, Eq. (21) can be rewritten in the following matrix form.

$$[\mathbf{GP}][\mathbf{c}'_p] = [\mathbf{RH}] \tag{24}$$

where

$$\mathbf{GP}_{ij} = \frac{\partial g_i}{\partial c_{pj}}, \quad \mathbf{c}'_{pj} = \frac{dc_{pj}}{d\tau}, \quad \mathbf{RH}_i = \text{right hand side of Eq. (21)}$$

Since the matrices [**GP**] and [**RH**] are known with given trial concentrations at each interior OC point, the vector $[\mathbf{c}'_p]$ can be easily determined from Eq. (24). Using this approach, we can deal with complex nonlinear isotherms here without any iteration.

3.3 *Isotherm Expressions*

The numerical procedure discussed above can accommodate any type of nonlinear isotherms as long as they do not cause mathematical singularities. The following two common types of isotherms are used in this work.

(1) Langmuir Isotherm

$$C^s_{pi} = \frac{a_i C_{pi}}{1 + \sum_{j=1}^{Ns} b_j C_{pj}} \quad \text{i.e.,} \quad c^s_{pi} = \frac{a_i c_{pi}}{1 + \sum_{j=1}^{Ns} (b_j C_{0j}) c_{pj}} \tag{25}$$

where $a_i = C^\infty b_i$. Note that $b_j C_{0j}$ can be treated as a dimensionless group for each component. With this the entire model system can then be treated with dimensionless parameters alone. This helps reduce the total number of parameters involved in discussions.

(2) Stoichiometric Isotherm with Constant Separation Factors

$$\bar{C}_i = \frac{\bar{C} C_i}{\sum_{j=1}^{Ns} \alpha_{ji} C_j} = \frac{\alpha_{i,Ns} \bar{C} C_i}{\sum_{j=1}^{Ns} \alpha_{j,Ns} C_j} \tag{26a}$$

where $\alpha_{ij} = 1/\alpha_{ji} = \alpha_{ik}\alpha_{kj}$, and $\alpha_{ii} = 1$. C_i is the concentration of ion component i in the stagnant fluid inside particles. $\bar{C}$ is the saturation capacity and is considered equal for all components. $\bar{C}_i$ is the concentration of ion component i in the solid of the particles. This type of isotherm is widely used in ion exchange and all the concentrations are based on the unit volume of the column rather than on the respective phases as in the case of Langmuir isotherms [3].

The stoichiometric isotherm can be converted into the isotherm shown below, which is the same algebraic expression as the Langmuir isotherm except that the "1 + " in the denominator of the Langmuir isotherm expression is dropped.

$$C^s_{pi} = \frac{a_i C_{pi}}{\sum_{j=1}^{Ns} b_j C_{pj}} \quad \text{i.e.,} \quad c^s_{pi} = \frac{(a_i/C_{0i}) c_{pi}}{\sum_{j=1}^{Ns} b_j c_{pj} C_{0j}/C_{0i}} \tag{26b}$$

The following relationships are needed for the conversion.

$$b_i = \alpha_{i,Ns} \quad \text{and} \quad a_i = b_i C^\infty = \frac{\alpha_{i,Ns} \bar{C}}{(1 - \varepsilon_b)(1 - \varepsilon_p)} \quad (i = 1, 2, \ldots, Ns)$$

where ion component Ns is assigned as the basis of the separation factors. Note that the units of a_i and b_i in the Langmuir isotherm and the converted stoichiometric isotherm are not the same. In the stoichiometric isotherm, the concentrations of components cannot all be zero at the same time, which means that the column is never "empty."

4 Efficiency and Robustness of the Numerical Procedure

The solution to the rate model provides the effluent history and the moving concentration profiles inside the column for each component. The concentration profile of each component inside the stagnant fluid phase and the solid phase of the particle can also be obtained, but they are rarely used for discussions.

Generally speaking, one interior collocation point (N = 1) is sufficient in some cases, while more often N = 2 is needed, especially when D_{pi} values are small, which in turn give large Bi_i and small η_i values. N = 3 is rarely needed. The number of elements Ne = 5–10 is usually sufficient for systems with non-stiff or slightly stiff concentration profiles. For very stiff cases, Ne = 20–30 is often enough.

Insufficient N tends to give diffused concentration profiles as shown in Figs. 3 to 5. Using N = 1 instead of N = 2 in Figs. 3 to 5 (dashed lines) saves about 60% CPU time on a SUN 4/280 computer, but the concentration profiles differ to some extent from the converged ones (solid lines). In Fig. 5, the dotted lines are obtained by using three quadratic finite elements (Ne = 3) and one interior collocation point (N = 1) with a CPU time of only 13.2 seconds. Though the dotted lines show a certain degree of oscillation, they still provide the general shapes of the converged concentration profiles, which take 6.9 minutes of CPU time. This means that one may use small Ne and N values to get the rough concentration profiles very quickly and then decide what to do next.

The efficiency and robustness of the numerical procedure are further demonstrated by more simulated effluent histories for the discussions in the following parts of this chapter, including cases involving very stiff concentration profiles.

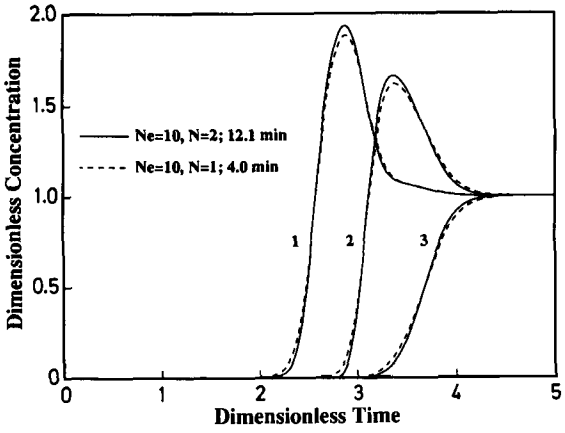

Fig. 3. Effect of the number of interior collocation points in the simulation of frontal adsorption

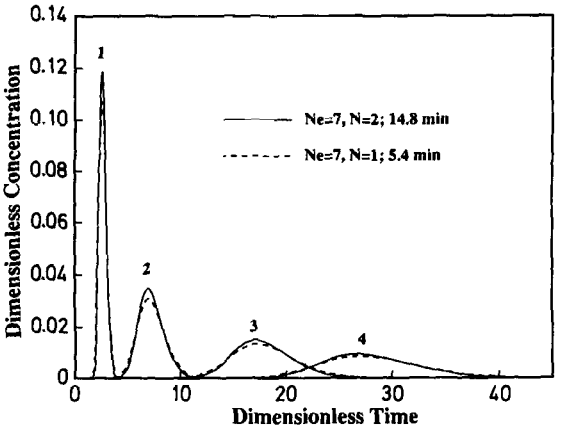

Fig. 4. Effect of the number of interior collocation points in the simulation of elution

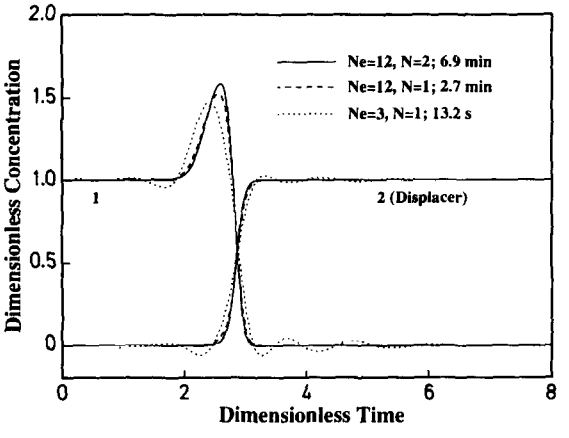

Fig. 5. Convergence of the concentration profiles of a stepwise displacement system

The FORTRAN code based on the numerical procedure discussed above is capable of simulating many kinds of multicomponent chromatographic processes, including frontal analysis, displacement development, simple nongradient elution, nonlinear gradient elution, and some multistage operations. Each mode of simulation is designated with a process index in the code, which is included in the data input.

The input data for the FORTRAN code contains the number of components, elements and interior collocation points, process index, time control data, dimensionless parameters, isotherm type and parameters. Note that the code is based on the dimensionless PDE systems and C_{0i} can be combined with b_i to

form a dimensionless group $b_i C_{0i}$. The initial conditions are reflected in the process index, or entered in the data file.

5 Extension of the Rate Model

The assumption that a local equilibrium exists for each component between the pore surface and the stagnant fluid phase in the macropores (Sect. 2.1) may not be satisfied if the adsorption and desorption rates are not high, or the mass transfer rates are relatively much faster. In such cases, isotherm expressions cannot be inserted into Eq. (2) to replace C^s_{pi}. Instead, a kinetic expression is often used. The so-called second order kinetics has been widely used to account for reaction kinetics in the study of affinity chromatography [31–33, 35, 36, 38]. A general rate model with second order kinetics has been applied to affinity chromatography by Arve and Liapis [38].

5.1 Addition of Second Order Kinetics

The second order kinetics assumes the following reversible binding and dissociation reaction.

$$P_i + L \underset{k_{di}}{\overset{k_{ai}}{\rightleftharpoons}} P_i L \tag{27}$$

where P_i is component i (macromolecule) and L represents the immobilized ligand. In this elementary reaction, the binding kinetics is of second order and the disassociation first order, as shown by the rate expression below.

$$\frac{\partial C^s_{pi}}{\partial t} = k_{ai} C_{pi} \left(C^\infty - \sum_{j=1}^{Ns} C^s_{pj} \right) - k_{di} C^s_{pi} \tag{28}$$

where k_{ai} and k_{di} are the adsorption and desorption rate constants for component i, respectively. The rate constant k_{ai} has a unit of concentration over time while the rate constant k_{di} has a unit of inverse time.

If the reaction rates are relatively large compared to mass transfer rates, then instant adsorption/desorption equilibrium can be assumed such that both sides of Eq. (28) can be set to zero, which consequently gives the Langmuir isotherms with the equilibrium constant $b_i = k_{ai}/k_{di}$ for each component.

Introducing dimensionless groups $Da^a_i = L\ (k_{ai} C_{0i})/v$ and $Da^d_i = Lk_{di}/v$ which are defined as the Damköhler numbers [54] for adsorption and desorption, respectively, Eq. (28) can be nondimensionalized as follows.

$$\frac{\partial c^s_{pi}}{\partial \tau} = Da^a_i c_{pi} \left(c^\infty - \sum_{j=1}^{Ns} \frac{C_{0j}}{C_{0i}} c^s_{pj} \right) - Da^d_i c^s_{pi} \tag{29}$$

If the saturation capacities are the same for all the components, at equilibrium, Eq. (29) gives $b_i C_{0i} = Da_i^a/Da_i^d$ and $a_i = C^\infty b_i = c^\infty Da_i^a/Da_i^d$ for the resultant multicomponent Langmuir isotherm. The Damköhler numbers reflect the characteristic reaction times with that of the stoichiometric time. The $b_i = k_{ai}/k_{di}$ values for affinity chromatography are often very large [32], but it is erroneous to jump to the conclusion depending on this alone that the desorption rate must be much smaller than that of adsorption, since the two processes have different reaction orders, and the concentration C_{pi} is often very small on the adsorption side as expressed by the first term on the right hand side of Eq. (28). It is obvious that the dimensionless Damköhler numbers provide a better comparison in this regard.

5.2 Solution Strategy

Adding the second order kinetics to the general rate model does not complicate the numerical procedure for its solution since the discretization process is untouched. One only has to add Eq. (29) in the final ODE system.

The following equation should be used to replace Eq. (21)

$$(1 - \varepsilon_p)\frac{\partial c_{pi}^s}{\partial \tau} + \varepsilon_p \frac{\partial c_{pi}}{\partial \tau} = \eta_i \sum_{k=1}^{N+1} \mathbf{B}_{l,k}(c_{pi})_k, l = 1, 2, \ldots, N \tag{30}$$

The final ODE system consists of Eqs. (17), (29) and (30). With the trial values of c_{bi}, c_{pi} and c_{pi}^s in the function subroutine in the FORTRAN code, their derivatives can be easily evaluated from the three ODE expressions.

If Ne elements and N interior collocation points are used for the discretization of the Eqs. (1) and (2), there will be Ns (2Ne + 1) (2N + 1) ODE's in the final ODE system, which are Ns (2Ne + 1) N more than in the equilibrium case. These extra ODE's come from Eq. (29) at each element node and each interior collocation point for each component.

The relationship among the kinetic effects, reaction equilibrium and mass transfer rates were discussed by Gu [72].

5.3 Addition of Size Exclusion Effects

In some chromatographic systems, large solute molecules have considerable size exclusion effects, which means that such large molecules either cannot access part of the small macropores in the particles or the entire particle at all. This is especially true in affinity chromatography in which large macromolecules are often present, and sometimes even larger complexes can be formed between the macromolecules with the soluble ligands. Size exclusion effects reduces the saturation capacity of a component with a large molecular size. A new isotherm system was developed recently by Gu et al. [55], for the study of adsorption systems with uneven saturation capacities as a result of size exclusion.

In recent years, there have been three ACS Symposium Series on size exclusion chromatography [56, 57, 58]. Several mathematical models have been proposed for size exclusion chromatography [59, 60, 61] among which the model proposed by Kim and Johnson is particularly helpful for this work. Their model is similar to the general rate model described in Sect. 1.2 of this work, except that their model considers size exclusion single component systems involving no adsorption. They introduced an "accessible pore volume fraction" to account for the size exclusion effect.

In this work, the symbol ε_{pi}^{a} is used to denote the accessible porosity (i.e., accessible macropore volume fraction) for component i. It implies that for small molecules with no size exclusion effect, $\varepsilon_{pi}^{a} = \varepsilon_p$, and for large molecules that are completely excluded from the particles $\varepsilon_{pi}^{a} = 0$. For any medium-sized molecules $0 < \varepsilon_{pi}^{a} < \varepsilon_p$. It is convenient to define a size exclusion factor $0 \leq F_i^{ex} \leq 1$ such that $\varepsilon_{pi}^{a} = F_i^{ex}\varepsilon_p$. F_i^{ex} is a function of the distribution coefficient of component i. It is also a function of the particle size distribution if the particle sizes cannot be assumed to be equal [60]. To include the size exclusion effect, Eq. (2) should be modified as follows.

$$(1 - \varepsilon_p)\frac{\partial C_{pi}^{s}}{\partial t} + \varepsilon_{pi}^{a}\frac{\partial C_{pi}}{\partial t} - \varepsilon_{pi}^{a} D_{pi}\left[\frac{1}{R^2}\frac{\partial}{\partial R}\left(R^2\frac{\partial C_{pi}}{\partial R}\right)\right] = 0 \tag{31}$$

where the first term $(1 - \varepsilon_p)\dfrac{\partial C_{pi}^{s}}{\partial t}$ should be dropped or set to zero, if a component does not bind with the stationary phase. It should be pointed out again that in the equation above C_{pi}^{s} values are based on the unit volume of the solids of the particles excluding the pores measured by the *particle porosity* ε_p. For a component which is completely excluded from the particles (i.e., $\varepsilon_{pi}^{a} = 0$), adsorbing only on the outer surface of the particles, Eq. (31) degenerates into the following interfacial mass balance relationship.

$$\frac{\partial C_{pi}^{s}}{\partial t} = \frac{3k_i}{(1 - \varepsilon_p)R_p}(C_{bi} - C_{pi,R=R_p}) \tag{32}$$

This equation can be combined with the bulk-fluid phase governing equation (Eq. (1)) to give the following equation which is similar to a lumped particle model.

$$-D_{bi}\frac{\partial^2 C_{bi}}{\partial Z^2} + v\frac{\partial C_{bi}}{\partial Z} + \frac{\partial C_{bi}}{\partial t} + \frac{(1 - \varepsilon_b)(1 - \varepsilon_p)}{\varepsilon_b}\frac{\partial C_{pi}^{s}}{\partial t} = 0 \tag{33}$$

where C_{pi}^{s} either follows the multicomponent isotherms or the expression for reversible binding, Eq. (28). If component i does not bind with the stationary phase, $C_{pi}^{s} \equiv 0$ and the fourth term in Eq. (33) is dropped for that component. As a reminder again, the solid phase concentration of component i, C_{pi}^{s}, is based on the unit volume of the solid part of the particle excluding pores, i.e., the unit

volume of the solid skeleton. The dimensional form of Eq. (33) is listed below.

$$-\frac{1}{Pe_{Li}}\frac{\partial^2 c_{bi}}{\partial z^2}+\frac{\partial c_{bi}}{\partial z}+\frac{\partial c_{bi}}{\partial \tau}+\frac{(1-\varepsilon_b)(1-\varepsilon_p)}{\varepsilon_b}\frac{\partial c_{pi}^s}{\partial \tau}=0 \tag{34}$$

5.4 Solution Strategy

If no component is totally excluded, the addition of the size exclusion effect in the rate models is very simple. One only has to use $\varepsilon_{pi}^a D_{pi}$ to replace $\varepsilon_p D_{pi}$ in the expressions of Bi_i and η_i, and to use $\varepsilon_{pi}^a c_{pi}$ to replace $\varepsilon_p c_{pi}$ in Eq. (10).

Mathematically, a singularity occurs in the model equation system when a component (say, component i) is totally excluded from the particles (i.e., $\varepsilon_{pi}^a = 0$) if one does not use Eq. (34) to replace Eqs. (9) and (10). It turns out that for numerical calculation, there is no need to worry about this singularity, if ε_{pi}^a is given a very small value below that of the tolerance of the ODE solver, which is set to 10^{-5} throughout this work. It is found that this treatment gives the results which have the same values for the first five significant digits as those obtained by using Eq. (34).

One should be aware that the size exclusion of a component affects its saturation capacity in the isotherm. It also affects the effective diffusivity of the component since the tortuosity is related to accessible porosity. It is clear that using size exclusion in a multicomponent model often leads to the use of uneven saturation capacities for a component with significant size exclusion and a component without size exclusion. This may cause problems when the multicomponent Langmuir isotherm is used in terms of thermodynamic inconsistency [55].

6 Other Extensions of the Rate Model

The general rate model can also be modified to account for the interaction between adsorbates and soluble ligands as in affinity chromatography. This extension is considerably more complicated. Details were given by Gu [72].

7 Study of Stepwise Displacement

Stepwise displacement chromatography has received considerable attention recently in microbiological processes for in situ removal of toxic product(s) [62, 63, 64]. Lee et al. [30], used a polyvinylpyridine (PVP) resin for the in situ removal of lactic acid during growth. This kind of in situ separation reduces

product inhibition, and thus enhances productivity. In such adsorption-combined processes, chromatographic columns are coupled with the bioreactor to remove the product(s) simultaneously via preferential adsorption and the adsorbate(s) is(are) then recovered through a displacement operation. This kind of stepwise displacement is also widely used to recover biomolecules from a dilute solution after they are adsorbed onto a column. In both cases, frontal adsorption proceeds the displacement process which often concentrates the adsorbate(s) by using a suitable displacer. This kind of stepwise displacement operation is somewhat different from the classical displacement chromatography or displacement development first classified by Tiselius [65] and extensively reviewed by Horvath and co-workers [11, 49, 66, 67].

Classical displacement chromatography was described by many researchers as a process in which a column packed with solid adsorbent is equilibrated with the mobile phase that has no or weak affinity to the adsorbent. A sample of mixtures is then introduced to the column. The sample usually takes up a fraction of the column volume in the inlet section. Subsequently, a development agent (called displacer) is pumped into the column. The displacer must have a higher affinity to the stationary phase than any of the components in the sample, i.e., its adsorption isotherm overlies those of the feed components [1, 67]. Provided that the column is sufficiently long, and isotherm curves are all favorably shaped, sample components will eventually migrate inside the column with the same speeds to form individual product zones. The series of such zones is usually called a displacement train [49, 66, 68, 69]. Figure 6 shows a displacement chromatogram with two sample solutes and one displacer. Parameter values used in simulation are listed in Table 1. Compared with elution chromatography, the displacement development has two distinct advantages: (1) the displacement effect reduces tailing (Fig. 6); (2) sample loading can be higher

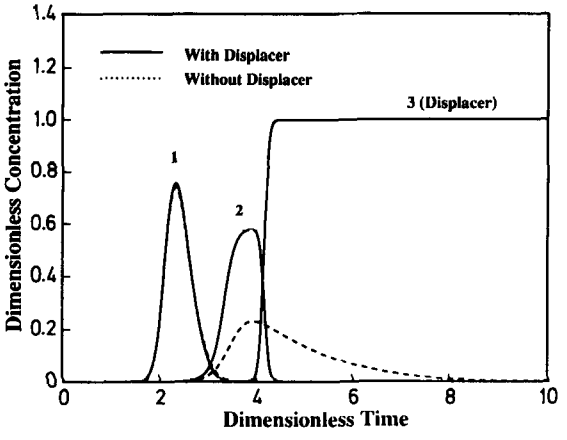

Fig. 6. Displacement chromatogram

Table 1. Parameter values used for simulation

Figures	Species	Physical Parameters					Numerical Parameters	
		Pe_{Li}	η_i	Bi_i	a_i	$b_i \times C_{0i}$	Ne	N
3	1	400	6	10	2	4 × 0.1	10	2
	2	400	6	10	7	14 × 0.1		
	3	400	6	10	15	30 × 0.1		
4	1	300	4	20	1.2	1.5 × 0.1	7	2
	2	320	4.2	17	8	10 × 0.1		
	3	400	5.5	16	24	30 × 0.1		
	4	500	7	15	38	48 × 0.1		
5	1	600	6	5	3	6 × 0.1	12	2
	2	600	3	6	12	24 × 0.3		
6	1	200	10	4	1	4 × 0.1	17	2
	2	200	5	6	5	20 × 0.1		
	3	400	5	6	30	120 × 0.1		
7	1	300	10	4	3	6 × 0.1	10	2
	2	300	15	4	4	8 × 0.3		
8	1	300	10	3	3	6 × 0.1	10	2
	2	300	15	4	4	8 × 0.11		
9	1	300	10	3	3	6 × 0.1	10	2
	2	300	15	4	2	4 × 0.4		
10	1	300	10	3	3	6 × 0.1	24	2
	2	300	15	4	30	60 × 0.3		

In all cases, $\varepsilon_b = 0.4$ and $\varepsilon_p = 0.5$. For Figure 4, $\tau_{imp} = 0.1$. The error tolerance of the ODE solver is tol = 10^{-5}. Double precision is used in the Fortran code

[11]. These features make the displacement development operation a very attractive alternative to elution in preparative scale chromatography [67].

The main difference between the displacement development and the stepwise displacement studied in this chapter is often the operation purpose itself. The former desires the products to be separated into a displacement train containing individual product zones in the effluent stream, while the latter requires the efficient displacement of the adsorbates. In other words, the desorption chromatography does not require a well-defined displacement train in the effluent; rather it requires the displacement of adsorbed component(s) with a minimum amount of displacer in a minimum length of time in order to obtain concentrated product(s). The product(s) in the effluent after displacement may be further purified if necessary after the stepwise displacement. A typical use of the stepwise displacement, as we have already mentioned, is the in situ separation during product formation [30, 62–64]. Another important difference is that the displacement development takes a sample which usually occupies only a fraction of the column inlet section while the stepwise displacement has no such

limitation. The strong affinity of the displacer which is required in the displacement development should not be mistaken as a requirement for the stepwise displacement.

7.1 Results and Discussion [70]

The multicomponent Langmuir isotherms (Eq. (25)) with uniform adsorption saturation capacities will be used in this study. For simplicity, only the two component displacement chromatographic processes will be discussed, in which component 1 is the component to be displaced and component 2 the displacer.

7.2 Effect of Feed Concentration of Displacer (C_{02})

Figure 7 shows that the higher the displacer concentration in the mobile phase, the higher the roll-up peak on the concentration profile of component 1 (see Table 1 for parameter values). This is due to the fact that a higher displacer concentration in the feed gives a faster migration rate for the concentration front of the displacer inside the column, a larger b_2C_{p2} value and, hence, a better displacement efficiency. Figure 8 shows a case in which the displacer does not give much help in the displacement of component 1 from the column because the concentration of the displacer is too low. This kind of situation was mentioned by some researchers [5, 71]. In Fig. 9, the affinity of the displacer is lower than that of the adsorbate. It shows that if the concentration of the displacer is sufficiently high a desirable displacement of the adsorbate can also be achieved. The study of the effect of ethanol concentration on the efficiency of the displace-

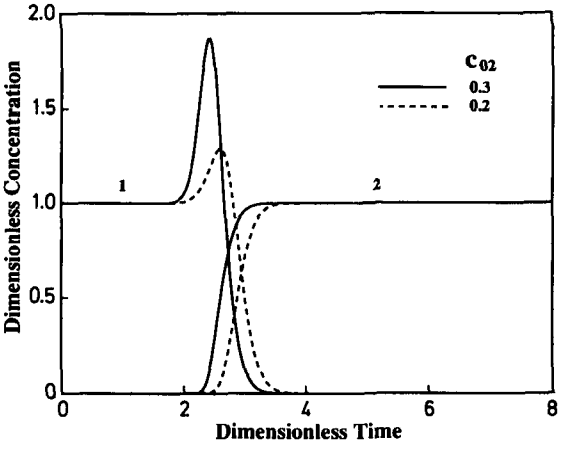

Fig. 7. Effect of displacer concentration on displacement

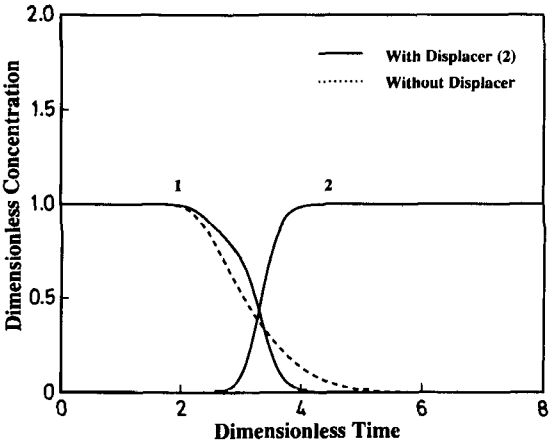

Fig. 8. Same conditions as Fig. 7, except that the concentration of the displacer is lower

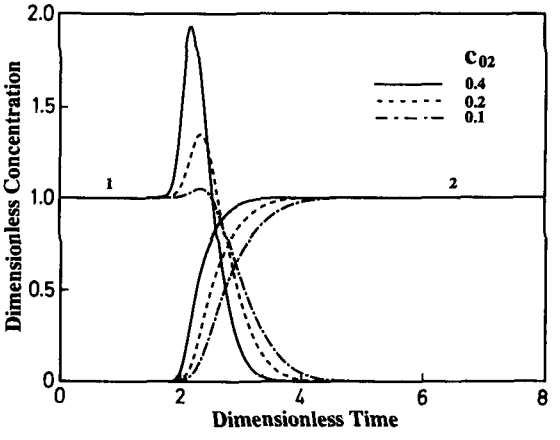

Fig. 9. Effect of displacer concentration on displacement for a case in which $b_2 < b_1$

ment of phenylalanine from a column packed with β-cyclodextrin-containing resin presented in Fig. 10 [72] qualitatively proved this argument. The affinity of ethanol with β-cyclodextrin is much smaller that phenylalanine, but when the ethanol concentration is sufficiently high, it still serves as an efficient displacer which gives good displacement results (Fig. 10).

7.3 Effect of Adsorption Equilibrium Constant of Displacer (b_2)

The effect of the b_2 value on displacement performance is shown in Fig. 11. It can be seen that an increase in b_2 delays the appearance of the roll-up peak,

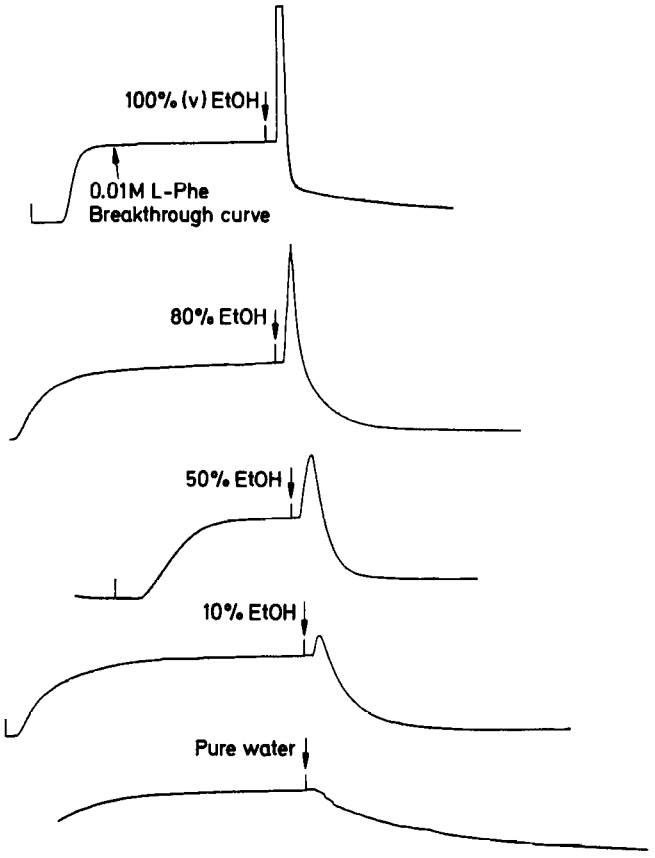

Fig. 10. Effect of ethanol concentration on displacement of phenylalanine

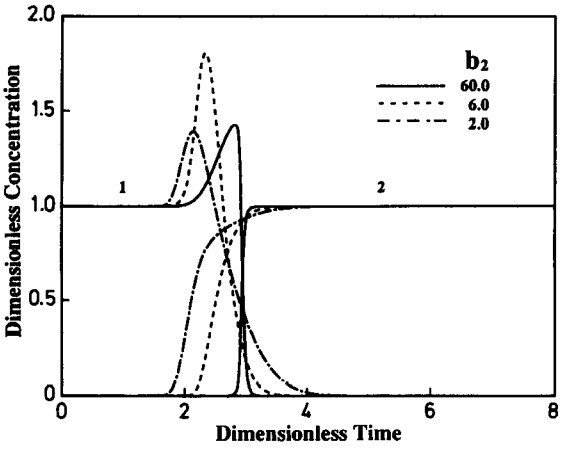

Fig. 11. Effect of b_2 on displacement performance

gives a sharper displacer front, and reduces the tailing of the displaced component. The maximum roll-up peak occurs somewhere in the middle range of the b_2 value. If the primary goal of displacement is to obtain a large fraction of pure component 1, a larger b_2 is obviously favorable. However, if the mixing of displacer in the product is not a setback, such as in the case when the displacer is a volatile organic solvent and the product is readily recovered by evaporation after the displacement, a larger b_2 is not always favorable. As a matter of fact, if the displacement is terminated when the major portion of the product has been recovered, then a small b_2 may be a better choice because the roll-up peak appears earlier.

Compared with the displacement development, the conclusion for stepwise displacement is somewhat different. The displacement development requires a displacer which has an affinity higher than any other component in the sample. However, this is hardly true for the stepwise displacement as we have already discussed in the cases of Figs. 9 to 11.

8 Summary

Among all kinds of models for nonlinear multicomponent chromatography, the general multicomponent rate model is the most comprehensive one. It accounts for various mass transfer mechanisms and nonlinear isotherms. It is a very useful tool for the study of the dynamics of nonlinear multicomponent chromatography. This chapter has presented an efficient numerical method for the solution and the extensions of the model. The model was used for the study of some interesting effects of isotherm characteristics of the displacer on the optimization of stepwise displacement. It was concluded that a displacer with a high feed concentration, and a suitable adsorption equilibrium constant is often a desirable choice when the purpose of the displacement operation is to displace and to concentrate the adsorbed species and to minimize the amount of displacer employed.

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