

Chapter 2

Literature Review

2.1 Theories for Nonlinear Multicomponent Liquid Chromatography

Many researchers have contributed to LC modeling. There exist a dozen or more theories with different complexities. A comprehensive review on the dynamics and mathematical modeling of isothermal adsorption and chromatography was given by Ruthven [1] who classified models into three general categories: equilibrium theory, plate models, and rate models.

2.1.1 *Equilibrium Theory*

According to Ruthven, the equilibrium theory of multicomponent isothermal adsorption was first developed by Glueckauf [2]. The interference theory by Helfferich and Klein [3] that is mainly aimed at stoichiometric ion-exchange systems with constant separation factors and the mathematically parallel treatise for systems with multicomponent Langmuir isotherms by Rhee and coworkers [4,5] are both extensions of the equilibrium theory.

Equilibrium theory assumes a direct local equilibrium between the mobile phase and the stationary phase, neglecting axial dispersion and mass transfer resistances. It effectively predicts experimental retention times for chromatographic columns with fast mass transfer rates (e.g., high resolution columns). It provides general locations, or retention times of elution peaks, but it fails to describe peak shapes accurately if mass transfer effects are significant. Equilibrium theory has been used for the study of multicomponent interference effects [3] and the ideal displacement development in LC [5]. Many practical applications have been reported [3,6–10].

2.1.2 Plate Models

Generally speaking, there are two kinds of plate models. One 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 cells, each with complete mixing. This gives a set of first-order ordinary differential equations (ODEs) that describes the adsorption and interfacial mass transfer between the bulk fluid phase and the particle phase. Many researchers have contributed to this kind of plate model [1,11–13]. However, plate models of this kind generally are not suitable for multicomponent LC since the equilibrium stages may not be assumed equal for different components. Thus, plate models are limited to single-component LC modeling.

The other kind of plate model is formulated based on distribution factors that determine the equilibrium of each component in each artificial stage. The model solution involves recursive iterations, rather than solving ODE systems. The most popular ones are the Craig distribution models. By considering the so-called blockage effect, the Craig models are applicable to multicomponent systems. Descriptions of Craig models were given by Eble et al. [14], Seshadri and Deming [15], and Solms et al. [16]. The Craig models have been used for the study of column-overload problems [14,17]. Velayudhan and Ladisch [18] used a Craig model with a corrected plate count to simulate elution and frontal adsorption.

2.1.3 Rate Models

Rate models refer to models containing a rate expression, or rate equation, which describes the interfacial 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 and the other for the particle phase. Different rate models have varying complexities [1].

2.1.3.1 Rate Expressions

The solid film resistance hypothesis was first proposed by Glueckauf and Coates [19]. 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. This simple rate expression has been used by many researchers [1,20–22] because of its simplicity, but this model cannot describe mass transfer details in the particle phase, which are important for larger particles used in preparative- and large-scale LC.

The fluid film mass transfer mechanism with a linear driving force is also widely used [1]. The driving force is the concentration difference of a component between

that on the surface of a particle and that in the surrounding bulk fluid. It is assumed that there is a stagnant fluid film between the particle surface and the bulk fluid. The fluid film exerts a mass transfer resistance between the bulk fluid phase and the particle phase, often called the external mass transfer resistance. If the concentration gradient inside the particle phase is ignored, the LC model then becomes a lumped particle model, which has been used by some researchers [23–25]. If the mass transfer Biot number, which reflects the ratio of the characteristic rate of film mass transfer to that of intraparticle diffusion, is much greater than unity, the external film mass transfer resistance can be neglected with respect to intraparticle diffusion. This is usually the case in LC operations using porous beads.

In some 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 and particle phases, and inside the particle phase in most chromatographic processes. The local equilibrium assumption here is different from that made for the equilibrium theory. The equilibrium theory assumes a direct equilibrium of concentrations in the solid and the liquid phases without any mass transfer resistance.

If the adsorption and desorption rates are not sufficiently high, the local equilibrium assumption is no longer valid. A kinetic model must be used. Some kinetic models were reviewed by Ruthven [1] and Lee [26]. Second-order kinetics has been widely used in kinetic models for affinity chromatography because affinity binding and dissociation reactions often suffer from slow kinetics. Thus, the reactions may not be assumed to be at equilibrium for accurate modeling [27–34].

2.1.3.2 Governing Equation for the Bulk-Fluid Phase

The governing partial differential equation (PDE) for the bulk-fluid phase can be easily obtained from a differential mass balance of the bulk-fluid phase for each component. Axial dispersion, convection, transient, and the interfacial flux terms are usually included. Such equations themselves are generally linear if physical parameters are not concentration dependent. They become nonlinear when coupled with a rate expression involving nonlinear isotherms or second-order kinetics.

For some rate models, such as models for isothermal, single-component systems with linear isotherms, analytical solutions may be obtained using the Laplace transform [1]. For more complex systems, especially those involving nonlinear isotherms, analytical solutions cannot be derived. Numerical methods must be used to obtain solutions to complex rate models that consider various forms of mass transfer mechanisms with nonlinear isotherms. Detailed rate models are becoming increasingly popular, especially in the study of preparative- and large-scale LC. With today's fast personal computers, there is no need to simplify a model to make it solvable. Simplified models often have mass transfer parameters that are nonstandard, which means they lack existing correlations for their estimation.

In this book, all the numerical solved LC models are full-blown mass transfer models as discussed below. This makes their mass transfer parameters fully compatible with classical transport phenomena theories for mass transfer in the chemical engineering literature.

2.1.3.3 General Multicomponent Rate Models

A rate model that considers axial dispersion, external mass transfer, intraparticle diffusion, and nonlinear isotherms is called a general multicomponent rate model. Such a model is adequate in most cases to describe the adsorption and mass transfer processes in multicomponent chromatography. In some cases, surface adsorption, size exclusion, and adsorption kinetics may have to be included to give an adequate description of a particular system. Although particle sizes and shapes used in an LC column are usually not uniform, except in some rare cases with uniform spherical silica beads, an average particle diameter can be used for modeling. Some researchers have used models with a particle size distribution term [35], but this treatment makes parameter estimation for mass transfer coefficients overly complicated since mass transfer correlations usually use a single particle diameter value. In the particle phase, pore diffusion and surface diffusion mechanisms can both be modeled. However, surface diffusion coefficient is usually not available [36]. An “effective” diffusivity is more conveniently used to cover both mechanisms without involving the specifics, although such diffusivity may be concentration dependent [36]. Parameter sensitivity analysis can always be carried out through computer simulation. It is possible that changes in some mass transfer parameters do not cause significant deviations in simulated effluent profiles because other parameters such as isotherm parameters, bed voidage, and particle porosity are far more sensitive, or the mass transfer parameters are already in the insensitive region to start with.

2.1.3.4 Numerical Solutions

A general multicomponent rate model consists of a coupled PDE system with two sets of mass balance equations, one for the bulk-fluid phase and one for the particle phase for each component. Several groups of researchers have used different numerical procedures to solve various general multicomponent rate models [37–40]. The finite difference method is a simple numerical procedure that can be directly applied to the discretization of the bulk-fluid phase PDE and the particle phase PDE [39,41]. To achieve a stable solution with a good accuracy, a huge number of discretization points are needed for a relatively stiff case. This is computational demanding. Its efficiency and accuracy are not competitive compared with other more advanced numerical methods, such as orthogonal collocation (OC), finite element (FE), or orthogonal collocation on finite element (OCFE) methods. To write an LC simulator for a specific project, simplicity may be a

major concern. Computation time is less important. However, if one wants to create LC software for broad applications with repeated simulation runs that may cover very stiff systems, an efficient numerical method is critical. This is why commercial software such as those for computational fluid dynamics use finite element and finite difference is never an option.

For the particle phase-governing equation, the OC method is the obvious choice. It is a very accurate, efficient, and relatively simple method for the discretization of a particle. It has been widely used with success for many particle problems [42,43]. The formulation of the OC method for particles is readily available in Finlayson's book [43].

Unfortunately, concentration gradients in the bulk-fluid phase can be very stiff; thus the OC method is no longer a desirable choice since global splines using high-order polynomials are computationally very expensive [43] and sometimes not stable. The method of OCFE uses linear finite elements for global splines 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 [43].

The FE method with 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, as in radial flow chromatography and nonisothermal adsorption with or without chemical reactions. Chromatography of some biopolymers also involves a variable axial dispersion coefficient [44]. The FE method is used throughout this book for the discretization of the bulk-fluid phase PDE.

2.1.3.5 Solution to the ODE System

If the FE method is used for the discretization of the bulk-fluid phase PDE and the OC method for the particle phase equations, an ODE system is produced from the LC model equations. The ODE system with initial values can be readily solved using an ODE solver such as subroutine "IVPAG" of the commercial IMSL software package [45], which uses the Gear's stiff method [40]. Another choice is the public domain Variable coefficient ODE (VODE) solver [46] freely available for download from <http://computation.llnl.gov/casc/software.php>. Because the ODE system is solved as an initial value problem, there is no need to treat the isotherm equations as algebraic equations with unknowns that have to be coupled with the ODEs to create an equation system coupling both ODEs and algebraic equations. That approach would require an ODE-algebraic equation solver that is less efficient than the more commonplace ODE solvers. The author initially used IVPAG, but later successfully switched to VODE to avoid the use of a commercial software package.

2.2 Scale-Up in Liquid Chromatography

Currently, LC scale-up is carried out largely based on trial-and-error and experience, with the help of some general scale-up rules that are not necessarily accurate [47]. Some of these rules were discussed by Snyder and Kirkland [48], Ladisch [47], and others [1,45,49]. They are mostly empirical or semiempirical relationships about particle size, flow rate, column length, and resolution. The correlations are more of a “rule of thumb” nature when they are used for scale-up. Knox and Pyper [50] did an extensive study on column overload. Some of their results on concentration and volume overload are also helpful in the scale-up of LC. There are many papers in this area.

Instead of following these scale-up rules, a rate model can be used to simulate chromatograms of a larger column a priori, i.e., before it is built or purchased. The model uses only few experimental data from a small column with the same packing as a large column. This step is necessary unless packaging structure data such as bed voidage and particles porosity, as well as isotherm parameters, are already available. Although rate models hold great potentials in more accurate scale-up of liquid chromatography, most papers in the literature have been on the investigation of LC behaviors and simulation of smaller columns to match experimental chromatograms. This book attempts to describe parameter estimation methods and modeling steps that lead to a priori predictions of the performances of larger LC columns based on some experimental work [51–53]. It is hoped that more and more chromatographers will come to realize that it is actually not that difficult to use the software for various LC models in this work for scale-up of LC after digesting the examples in this book. There is no need for them to get involved in the details of the numerical methods since the models have already been solved. However, an understanding of the effects of isotherm parameters and mass transfer-related parameters is essential.

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