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Modeling and Multi-Objective Optimization of a Chromatographic System

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13.1 Introduction

Chromatography is a versatile separation technique whose utility was first demonstrated by Tswett [1] at the beginning of the last century. It can separate almost any mixtures with great precision and has found significant applications in the laboratories of analytical chemists and biologists because of its separation prowess. Application of chromatography as an industrial process in the mainstream chemical industries, however, is still limited mainly because of economic factors. In general, chromatographic operations can be costly. Few products are valuable enough and their separation difficult enough to justify the employment of chromatography as a process option. The most important large-scale applications of chromatography are found in the industrial separations of p-xylene, o-xylene and ethylbenzene from light petroleum reformates [2], and in the separation of fructose and dextrose from corn syrup. The most prevalent industrial application of chromatography is currently found in the pharmaceutical and fine-chemical industries. The amounts of purified product typically produced by these industries are far less than the outputs of the bulk-chemicals, but these are high-value products that can bear the cost of chromatographic separations. The purity requirements of these industries are generally very high, and quite often chromatography is the most economic, if not the only available option to purify these products.

Multi-Objective Optimization in Chemical Engineering: Developments and Applications, First Edition.
Edited by Gade Pandu Rangaiah and Adrián Bonilla-Petriciolet.

In the pharmaceutical industry, chromatography is widely applied in the separation of stereo-isomers and the mixtures of biomolecules. Stereo-isomers are isomeric molecules having the same molecular formula and the same sequence of bonded atoms, but are only different in the 3D orientations of their atoms in space [3]. Any one of the two stereo-isomers is called an enantiomer. Enantiomers of a molecule, although having identical physical and chemical properties, often lead to different chemical reactions with another pair of enantiomeric molecules. For drug molecules, for example, often only one of the enantiomers is responsible for the desired physiological benefits. The other enantiomer can be either less active, inactive, or sometimes lead to adverse side-effects. The last possibility becomes the most important criterion during the drug development period and each candidate drug molecule should be tested for their enantiomeric activities.

Synthesis of a particular enantiomer is possible but may require a significant investment of time and money [4]. A more economically acceptable route is to synthesize a racemate, which is a mixture of equal amounts of the enantiomers, and separate them to get both the enantiomers as products. The separation route is particularly important during the drug-development period where both the enantiomers have to be tested for the toxicological and early clinical trials. During the drug development period the main focus stays on taking the drug to the market at the earliest. The enantiomers of a huge variety of intermediates and APIs (active pharmaceutical ingredients), at each stage of drug trial, need to be separated in gram to kilogram scale in the shortest possible time. Chromatography has emerged as the most important process for enantiomeric separation. Another important application of chromatography is in the separation of biomolecules. Biomolecules, such as proteins and peptides, are increasingly being used as drug and therapeutic substances. Separation of the target biomolecules from a plethora of impurities is a challenging task, which consumes majority of the production cost. Although several separation mechanisms are used, for example centrifugation, chromatography plays the central role in the downstream process line, often consuming the maximum percentage of the production cost.

The operating conditions of the chromatographic systems in these industries are often designed based on the methods developed during the analysis of the compounds in laboratories. As the optimum separating conditions at the analytical scale, where mixtures are handled under very dilute conditions, should normally be different from the optimum conditions for separating the concentrated mixtures, direct transfer of laboratory methods to the separation bench does not lead to optimum operation. Experimental trial-and-error methods, supported by experience, can be certainly applied to improve the separating conditions, but that would need a significant investment of time and materials.

Under such time and material constraints, developing the optimum separation conditions may not be given priority. Even after a certain molecule is approved as a drug substance, developing optimum operating conditions in the production stage is not an option because the regulatory authorities approve the production route along with the new molecule, giving little opportunity for later improvement of the separation performance. A model-based optimization study, under such circumstances, can be useful in developing optimum operating conditions in a shorter period of time and employing far fewer resources compared to the experimental trial-and-error methods. This can be done during the initial evaluation of the APIs, which will not only require less time to develop sufficient materials for drug trial but even later in the production stage it can lead to significant economic benefit. This chapter will present a comprehensive account for developing such a model-based optimization platform, which can be employed for optimization studies of different chromatographic processes.

13.2 Chromatography—Some Facts

The separation mechanism of chromatography uses dissimilarities in the equilibrium distribution of a mixture's molecules between a stationary and a mobile phase. The main characters of a chromatographic system are (i) the stationary phase, (ii) the mobile phase and (iii) the mixture of the components to be separated. The definitions of the stationary and the mobile phases are rather broad. A stationary phase does not need to be a solid entity. For example, a liquid phase can be immobilized through grafting on solid particles to prepare a stationary phase. The mobile phase, as the name suggests must be a fluid, either gaseous, liquid or supercritical. Depending on the nature of the mobile phase, chromatography is referred as gas chromatography (GC), liquid chromatography (LC) or supercritical fluid chromatography (SFC). Similarly, depending on the surface properties of the stationary phase, chromatographic methods can be classified as normal-phase (NP), reversed-phase (RP), ion-exchange (IEx) and other varieties of chromatography. Please note that often the chromatographic operations are associated with adsorption because in many instances chromatography does use the adsorption phenomenon of solute molecules on a stationary phase to carry out the separation. Chromatography, however, is not necessarily only an adsorption-based separation technique; rather adsorption is one of the physical phenomena utilized in chromatographic operations for separation. For example in ion-exchange chromatography the ion-exchange phenomenon is used to attach the solute molecules preferentially to the stationary phase. Secondly, the main difference between the operations of the standard *adsorption* separations and *chromatographic* separations lies in the mobility of the solute molecules in the mixture. In adsorption, generally one or more of the molecules is arrested by the stationary phase while the other molecules pass through. In chromatography, on the other hand, all the molecules are allowed to move, but at different speeds, which is why it is also called a separation based on differential migration. Throughout the rest of the chapter the word *attachment* of the solute molecules to the stationary phase will be used to indicate any behavior leading to an interaction of the solute molecules with the stationary phase, be it adsorption, ion exchange, liquid-liquid partitioning or any such phenomena.

In this chapter we will only discuss to liquid chromatography. So, any reference to mobile phase here should be understood as the liquid mobile phase. In liquid chromatography, at the beginning of the chromatographic operation, the mixture to be separated should be dissolved in the mobile phase. The stationary phase, which is most commonly a cylindrical column packed with porous particles, is percolated continuously with the mobile phase. When the solution containing the mixture is injected at the entrance of the column, the mobile phase carries the component molecules, imparting a net force in the axial direction on the mixture molecules, as shown in Figure 13.1. The affinity of the mixture molecules to the stationary phase, on the other hand, retards their movement and the component molecules tend to spend different lengths of time adsorbed on the stationary phase and flowing with the mobile phase, controlled by the equilibrium constant. Depending on the relative affinity, different component molecules of the mixture spend different lengths of time in the mobile and stationary phases. Understandably, the molecules spending more time in the mobile phase elute earlier, compared to others. This differential migration of the component molecules leads to separation. Schematic diagrams of the migration of different components are shown in Figure 13.1. The upper part of the right hand side of the figure shows the migrating component bands inside the column, whereas the lower part shows the elution profile of the components as a function of time.

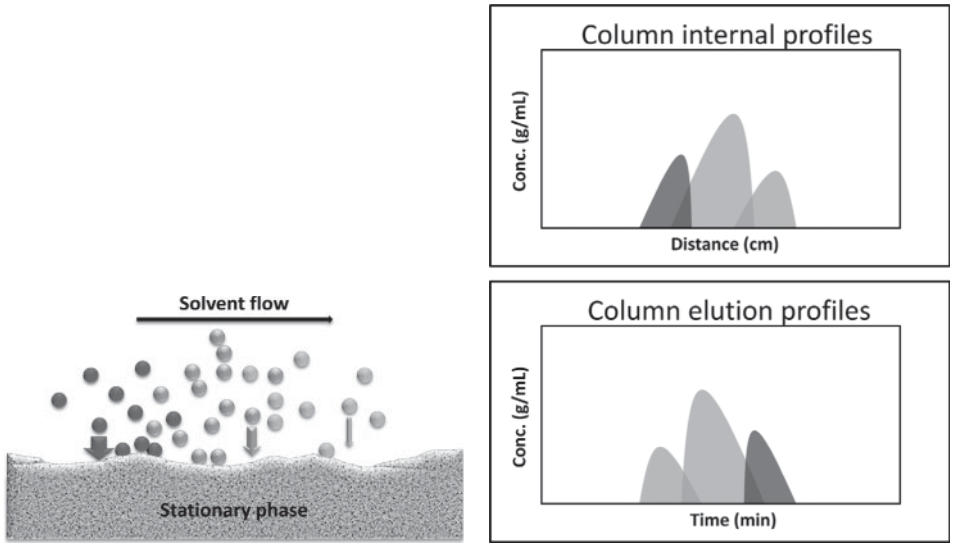

Figure 13.1 *Schematic representation of the differential migration of the component molecules of a mixture in chromatography. The black arrow shows the direction imparted by the solvent and the coloured arrows show the direction of attraction of different molecules towards the stationary phase. The width of the arrow represents the power or the affinity of attraction. The internal profiles, shown at the top of RHS is the chromatographic representation of the migrating molecules, which can be followed by the colours of the profiles. The elution profiles (RHS bottom), on the other hand, shows the way the bands of the separated molecules exit the column.*

The two main physical phenomena that occur inside a chromatographic system are the thermodynamic equilibrium between the component molecules in the mobile phase and those adsorbed on the stationary phase. This phenomenon, as mentioned above is the main mechanism of separation in chromatography. The component molecules, however, cannot establish an instant equilibrium. In between the thermodynamic interactions between the mobile and the stationary phase, the molecules diffuse around the central band, which leads to remixing of some of the separated molecules. So, while the thermodynamic interactions lead to separation of the component molecule, the transport phenomena lead to destroying the separation. Modern chromatographic columns, however, can handle this issue. In columns packed with fine particles the effect of transport phenomena, although measurable, is never significant enough to completely disrupt a separation. However, it is also not negligible and must be accounted for.

A modern chromatographic setup is shown schematically in Figure 13.2. This shows that more than one of the solvents (shown as A, B and C) can be employed during a chromatographic operation to prepare the mobile phase. The composition of the mobile phase can be even varied during the operation by mixing different volumes of the solvent from the sources. After the solvent is mixed, which can be done before or after the pump, the mobile phase is led to an injector unit. In the injector, which is placed just before the chromatographic column, a precise volume of the mixture solution is injected into the

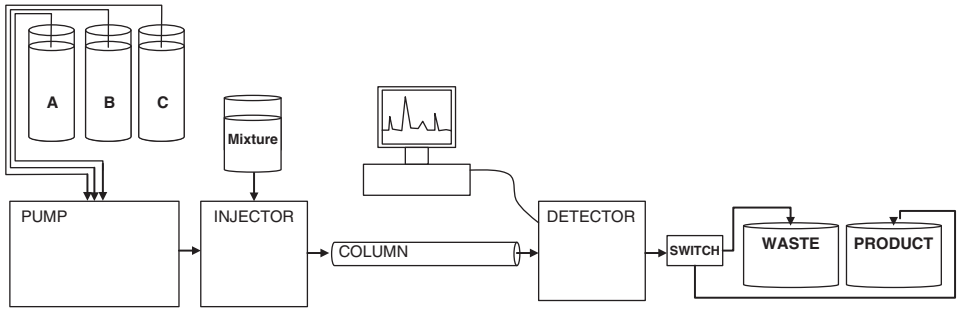

Figure 13.2 *Schematic diagram of a modern chromatographic setup.*

mobile phase. The mixture solution is then percolated through the column dissolved in the mobile phase, leading to chromatographic separation. A detector is placed after the column and the eluted mobile phase is taken through the detector. There can be different detection mechanisms, among which UV detection, which exploits the absorbance of ultraviolet light by the eluting compounds, is the most commonly used method. For chromatographic separation, the eluting solvent is collected at the precise times when the target compound is eluting guided by the signals detected in the detector. The final product is then collected through vacuum evaporation of the solvent.

13.3 Modeling Chromatographic Systems

Chromatography involves complex movement of the mixture molecules through the stationary phase. The mobile phase, while percolating through the bed of porous particles, carries the component molecules, which diffuse in and out of the particle pores, undergo thermodynamic interactions with the stationary phase, and eventually elute out of the column along with the mobile phase. So, fluid dynamics, mass-transfer phenomena, and equilibrium thermodynamics play important roles in the chromatographic operation [2]. Figure 13.3 shows the various transport paths that the component molecules follow during their movement through the chromatographic bed. Outside the particles, movements of the component molecules are controlled by the momentum of the mobile phase and also the diffusion movements of these molecules in the axial direction, which is indicated by “1”. To enter the particle pores, the component molecules first have to overcome a barrier of a stagnant film of mobile phase on the particles through a mass-transfer mechanism, which is indicated by “2”. Inside the pores, the molecular movement is controlled only by diffusion, which is indicated by “3”.

To model a chromatographic system, different levels of abstraction can be adopted to model transport behavior. A detailed model, which takes into account all the separate contributions of the axial diffusion, the film mass-transfer, and the pore diffusion, is called the general rate (GR) model. A less rigorous model, which assumes that the film mass transfer is the rate limiting step for the molecules going inside the pores, combines the film mass transfer and the pore diffusion into a single transport effect, and is called the lumped kinetic (LK) model. A further approximation of the transport properties, combining the

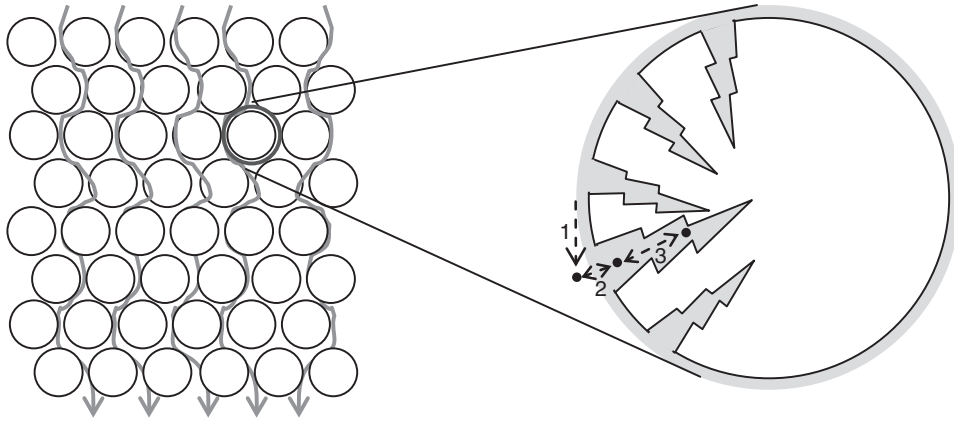

Figure 13.3 *Schematic diagram of the diffusion and mass-transfer phenomena experienced by a molecule inside a chromatographic system, while travelling in and out of the porous particles.*

contributions of all the transport behaviors into a single *apparent diffusion coefficient*, is done in the equilibrium dispersive (ED) model.

The main factor behind selecting any one of these models for a simulation study is the diffusion coefficient of the component molecules of the mixture. For large biomolecules, such as proteins, which have slow diffusion coefficients, the GR model is the best to work with, because neither the pore diffusion nor the film mass transfer is fast enough to be neglected or combined into one entity. On the other hand, for relatively smaller molecules, whose diffusion rates are quite fast, the ED model is sufficient to work with. For the molecules with intermediate size, roughly ranging from 500 to 15 000 Da, the LK model should be a convenient choice. In the current chapter, the LK model will be considered because of its wider applicability in modelling separation systems for biomolecules of different sizes.

The basic mass-balance equation of the LK model can be written as

$$\frac{\partial c_i}{\partial t} + \frac{(1-\epsilon)}{\epsilon}\frac{\partial q_i}{\partial t} + \frac{u}{\epsilon}\frac{\partial c_i}{\partial x} = \frac{D_{a,i}}{\epsilon}\frac{\partial^2 c_i}{\partial x^2} \; homogeneous \tag{13.1}$$

where,

c_i = concentration of component i in the mobile phase (g/mL);
q_i = concentration of component i in the adsorbed phase (g/mL);
ϵ = void fraction of the chromatographic column (-);
u = velocity of the mobile phase (cm/min);
$D_{a,i}$ = apparent diffusion coefficient of component i (cm^2/min);
x = the space co-ordinate (cm);
t = the time co-ordinate (min);
i = component index, $i \longrightarrow 1$, *number of components*.

The concentration of the adsorbed phase (q_i) is related to the equilibrium concentration ($q_i{}^*$), and the term $\frac{\partial q_i}{\partial t}$ in Equation 13.1 can be written as:

$$\frac{\partial q_i}{\partial t} = k_{m,i}(q_i{}^* - q_i) \tag{13.2}$$

where $k_{m,i}$ = the mass transfer coefficient of component i across the stagnant film (1/min).

In this model the equilibrium concentration ($q_i{}^*$) is basically the concentration at the interface of the mobile phase and the stagnant film around the stationary phase. It is assumed in the model that $q_i{}^*$ is in equilibrium with the mobile-phase concentration, c_i, whereas the solid-phase concentration (q_i) is controlled by the mass-transfer coefficient k_m and the equilibrium concentration, as expressed in Equation 13.2.

To quantify the thermodynamic interaction between the component molecules in the mobile and in the stationary phases, a mathematical formulation called the equilibrium isotherm is used. These thermodynamic interactions could be very different in nature, such as the interactions in an ion-exchange system, or the interactions in reversed-phase system where the stationary phase is silica grafted with nonpolar octadecyl carbon chains. Irrespective of the physical nature of interactions between the solute and the stationary phases, the equilibrium isotherm tries to quantify the relationship. Mathematically, the equilibrium isotherms express the concentration $q_i{}^*$ as a function of the mobile-phase concentrations, c_i. In general, in any chromatographic system handling concentrated solutions of the mixture molecules, the concentration $q_i{}^*$ is controlled by the mobile phase concentrations of *all* the component molecules. So the general expression of the equilibrium isotherms, or simply isotherms, is:

$$q_i{}^* = f(\bar{c}) \tag{13.3}$$

More specific expressions of the isotherms are discussed below.

The initial and the boundary conditions of the set of partial differential equations (Equation 13.1) are:

Initial conditions:

$$t = 0 \longrightarrow c_i = 0, \quad q_i = 0, \quad q_i^* = 0 \tag{13.4}$$

Boundary conditions:

$$x = 0, \frac{\partial c_i}{\partial x} = \frac{u}{D_{a,i}}(c_i - c_{in,i}) \tag{13.5}$$

$$x = 1, \frac{\partial c_i}{\partial x} = 0 \tag{13.6}$$

The feed conditions are expressed as:

$$x = 0, c_{in,i}(t) = c_{f,i} \longrightarrow when, t \leq t_f \tag{13.7}$$

$$x = 0, c_{in,i}(t) = 0 \longrightarrow when, t > t_f \tag{13.8}$$

Where, $c_{in,i}$ is the inlet concentration of component i to the column and $c_{f,i}$ is the feed concentration of component i.

The above set of equations is valid only when the operations are carried out in isothermal conditions, which is true for most of the separation problems discussed here. The further assumptions used to derive these equations are as follows [2]:

- The column is radially homogeneous and all the variations take place only in the axial direction. This assumption is valid for most of the industrial columns with the modern packing mechanisms.
- The mobile phase compressibility is negligible. Within the pressure and temperature ranges used in LC the mobile phase compressibility is sufficiently low to be considered as incompressible.
- The mobile phase viscosity is constant throughout the system.
- The axial dispersion coefficient is constant throughout the column.
- The partial molar volume of the mixture components is the same in the mobile and in the stationary phases.

13.4 Solving the Model Equations

There can be different ways of numerically solving the set of equations described in the previous section. To solve the chromatographic mass-balance equation, methods like finite difference and orthogonal collocation have been used and reported quite often in the literature [2]. In this section application of the finite-difference method, which is easy to construct and almost always leads to satisfactory solution, will be described in short.

In a batch chromatographic system, the concentration profiles of the component molecules inside a column are transient in nature (Equation 13.1), where all the related concentrations (c_i, q_i and q_i^*) are expressed as functions of space (x) and time (t), leading to a set of partial differential equations (Equation 13.1).

To solve the PDE numerically, the time and the space domain need to be discretized. Excellent solvers for initial value problems are available commercially and also from different research groups. In the current study the DIVPAG routine from International Mathematics and Statistics Library (IMSL) was used. DIVPAG can solve initial-value problems for ordinary differential equations using either Adams–Moulton's or Gear's *backward differentiation formula* (BDF) method. To use DIVPAG for solving the set of PDEs the x domain was discretized into a number of grids as shown in Figure 13.4. The concentrations inside the grids are assumed to be homogeneous and are functions of time. Note that by discretizing the x variable we could transform the PDE into a set of initial value ODE problems which can be solved by DIVPAG. Also note that in Figure 13.4, although only the

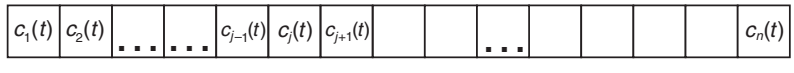

Figure 13.4 *Schematic diagram of the grids into which the space domain of the chromatographic column can be distributed. Accordingly, cell "1" represents the entrance of the column, whereas cell "n" the exit. Concentrations inside each cell is assumed to be homogeneous and functions of time, expressed by* $c_{1\to n}(t)$. *Only the mobile phase concentrations* (c_i) *are shown in the figure but similar considerations hold for* q_i *and* q_i^* *as well.*

expressions for the mobile phase concentrations are shown, they are valid for the adsorbed phase (q_i) and the equilibrium concentrations (q_i^*) as well.

The interrelationship between the grid concentrations can be formulated based on the main PDE (Equation 13.1). Following the backward difference method, the different terms of the mass balance equation (Equation 13.1) can be written as:

$$\frac{\partial c_i}{\partial x} = \frac{c_i|_{x=j} - c_i|_{x=j-1}}{\Delta x} \tag{13.9}$$

$$\frac{\partial^2 c_i}{\partial x^2} = \frac{c_i|_{x=j-1} - 2c_i|_{x=j} + c_i|_{x=j+1}}{\Delta x} \tag{13.10}$$

The time differential of the adsorbed phase concentration is expressed by Equation 13.2.

Combining the above equations, the time differential of the mobile phase concentrations can be written as:

$$\frac{\partial c_i}{\partial t} = \frac{D_{a,i}}{\epsilon}\left(\frac{c_i|_{x=j} - c_i|_{x=j-1}}{\Delta x}\right) - \frac{u}{\epsilon}\left(\frac{c_i|_{x=j} - c_i|_{x=j-1}}{\Delta x}\right) - \frac{(1-\epsilon)}{\epsilon}(k_{m,i}(q_i^* - q_i)) \tag{13.11}$$

Solving the above set of equations will provide the values of all the concentrations over the column as a function of time. The concentration at the last cell also represents the outlet concentration of the column and can be used as the elution profile.

To solve the above set of equations we need to know the transport parameters, i.e. $D_{a,i}$ and $k_{m,i}$ and the equilibrium isotherms (Equation 13.3). Direct calculation of these properties from the basic data could be possible. However, that may not be practical unless the measurement is done under the exact experimental conditions. For example, the transport properties used in the equations represent combinations of the solute diffusion under several restricted conditions. The pore diffusion takes place as hindered diffusion under the influence of the pore walls and may not be easy to calculate even if the bulk diffusion coefficients of the molecules are known. A convenient way to determine these parameters in a shorter time is to *fit* the experimental results with the model equations. The values of the parameters obtained in this way are true in a narrow range and may not represent any exact physical behavior, but they are still useful for solving the equations. The steps for the determination of the model characteristic parameters, which can be also called the model characterization, is explained in the next section.

13.5 Steps for Model Characterization

Selection of the experimental conditions for model characterization can be a challenging job. In the industrial scenario a sufficient supply of purified components may not be available a priori to design the purification process. The time frame available for the overall design of the process will be short, as discussed earlier. Ideally a small set of experiments must represent the entire search space so that a credible optimization study can be carried out, but involving minimum experimental efforts. In this section, a step-by-step method will be described which can be employed to characterize the mathematical model described in Equation 13.1.

13.5.1 Isotherms and the Parameters

The standard procedures discussed in the literature to determine equilibrium isotherms are numerous [2]. One of the most accurate techniques is the frontal analysis (FA). In FA the pure components are continuously fed into the column until the entire column is saturated. The adsorbed phase concentration can then be calculated from the breakthrough time of the pure component. This operation is carried out at different concentrations to determine the isotherm over the full range of the concentrations being used. In this procedure the the solid-phase concentrations can be directly measured as a function of the mobile-phase concentrations. The method is accurate but requires a considerable amount of purified components to start with. So, if enough time and purified components of the mixture are available at the beginning, one should employ the FA method to determine the single component isotherms. Then using a suitable method, such as ideal adsorbed solution (IAS) theory, the binary isotherm can be determined from the single component isotherms.

From an industrial perspective, however, availability of such time and materials is improbable. Under such situations a more appropriate method would be the so-called Inverse Method (IM). In the IM, pulses of the mixture solutions are first injected and passed through the column and their elution profiles recorded. Then simulated elution profiles are generated using the mathematical models, employing estimated isotherms and isotherm parameters. The simulated profiles are then compared with the experimental profiles and the difference between them calculated. Then using a minimization routine the isotherm and the isotherm parameter values can be updated and the best fitted value determined. The main difference between the IM and the other techniques is IM's better utilization of computational resources vis-a-vis the experimental efforts. This leads to faster determination of isotherm parameters, using significantly lesser amount of sample and solvent in the experimental studies, which is perfectly suitable from industrial perspectives.

The main problem of the IM, however, also originates from its strong dependence on the computational part. Users may often need deeper understanding of the tools, the simulation model and the optimization routines, especially their shortcomings, to make this method work properly. They should also have a fair idea regarding the plausibility of the fitted values. These problems arise mainly because of the *compensating effect* between the transport parameters and some of the isotherm parameters, which may enable different combinations of these parameters to simulate similar profiles. The compensating effect can be a common feature in many engineering optimization problems; a detailed discussion of this effect is available in reference [5]. In short, the compensating effect refers to the ability of a decision variable or a set of decision variables (say S1) to influence the objective(s) to reach a certain value, which can also be achieved by the influence of another decision variable or another set of decision variables (say S2). In such situations one can reach solutions that are numerically in order but physically unreasonably or erroneous.

This means that the fitting procedure is never straightforward and the optimizer may often need user intervention in guiding it towards the right solution. Very often the success of the IM depends on the initial guess regarding the equilibrium isotherm and the transport properties. In addition to the determination of the parameters, in the IM one has to start with the selection of the isotherm model a priori. Although there is no well defined rule, one can generally identify the isotherm by (i) noting the pattern in which the chromatographic band concentrations are eluting with increasing concentration of the feed solution or,

(ii) looking for some specialty in the band shapes, for examples long tailing or double shock formation. Various standard isotherms are discussed in the literature, describing a wide variety of elution profile shapes, from where one can select the best suited one. Any error or deliberate simplification in the selection of the isotherm model can enhance the possibility of errors from the compensating effect. The optimizer can try different (otherwise physically unacceptable) means to reduce the error. What it cannot achieve by changing the isotherm parameters (because of the choice of a wrong isotherm) it will try to achieve by changing other variables. For example, it may try to increase the diffusion coefficient to adjust a corner which is actually produced because of a thermodynamic effect in the experimental profile.

The success of the IM also crucially depends on the selection of the optimization routine, as this is what ultimately detects the values of the characteristic parameters through minimizing the difference between the experimental profiles and the simulation profiles. Several minimization techniques can be used for this purpose [2], which can be roughly divided into (i) deterministic methods, like the Conjugate gradient algorithm, the Marquardt method or the downhill Simplex method, and (ii) population-based stochastic methods, such as NSGA-II [6]. The codes of these optimization routines are freely available on the Internet. For example, the code for NSGA-II can be downloaded from the web site of Kanpur Genetic Algorithms Laboratory (KANGAL) at www.iitk.ac.in/kangal/codes.shtml (accessed December 9, 2012). The success of deterministic methods depends strongly on the selection of the initial guess values, which should be sufficiently close to the solution. For the population-based stochastic techniques, on the other hand, goodness of the initial estimate may not be a very strong criterion as one can supply a possible range of values within which the solution may lie. The situation, however, may be tough for the stochastic methods as well in some cases, especially when the compensating effect is high, which can take the solution towards local optima.

As a good initial estimate of the isotherm and the transport parameters are always helpful, in the following subsections some methods to calculate the initial estimates directly from the experimental profiles are provided. These methods have been developed based on the ideal approximation of the model equations and can give close estimates of the model parameters [2].

13.5.2 Selection of Isotherms

Before estimating the parameters of the isotherm we need to first select an isotherm model. In general, the isotherms can be classified in different ways based on the type of relationship between the mobile phase and the stationary phase concentrations. According to Brunauer *et al.* [7] the isotherms can be classified as Types 1 to 5. Among these, the most commonly encountered isotherms are probably Types 1, 2, 3 and 5. A schematic of the c versus q relationship and the corresponding elution profiles of these types are shown in Figure 13.5. Some representative isotherm equations from each of the types [8] follow.

1. The Langmuir isotherm assumes monolayer attachment of solute molecules to the available sites on the stationary phase to saturate the column [2]. The isotherm equation is expressed as:

$$q^0(c) = \frac{q_s K c}{1 + K c} \tag{13.12}$$

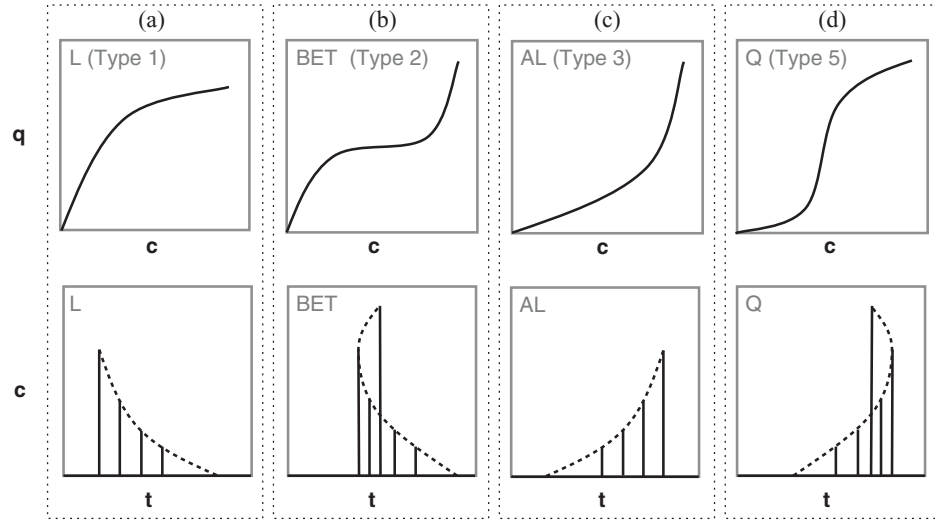

Figure 13.5 *A schematic diagram showing the liquid-phase versus solid-phase concentrations and the elution profiles as a function of time, with increasing overloading, for the following isotherms: (a) Langmuir (Type 1), (b) BET (Type 2), (c) anti-Langmuir (Type 3), and (d) Quadratic (Type 5).*

where q_s is the stationary phase concentration at saturation or the saturation capacity, and K is the equilibrium constant of the distribution of the solute molecules between the mobile and the stationary phases. The stationary phase concentration monotonically increases with the component concentration in the mobile phase, till it reaches the saturation capacity, as shown in Figure 13.5a.

2. The anti-Langmuir isotherm shows increasing stationary phase concentration with increasing component concentration in the mobile phase, which can increase towards infinity (Figure 13.5b). Such behavior is often expressed by the following equation:

$$q^0(c) = \frac{q_s K c}{1 - Kc} \tag{13.13}$$

In the above equation, the parameter q_s, although playing a similar role as in the Langmuir isotherm, does not carry any physical meaning. This is because the adsorbed phase concentration can grow indefinitely in anti-Langmuir isotherm and there cannot be any saturation capacity. Here the fluid phase concentration is limited to the range from 0 to $1/K$.

3. The Quadratic or the S-shaped isotherm. It shows a solute-stationary phase interaction similar to the anti-Langmuir isotherm at the low solute concentrations and a Langmuir-type behavior at higher concentrations beyond an inflection point (Figure 13.5d). The isotherm can be also derived from statistical thermodynamics and can be expressed as [2]:

$$q^0(c) = \frac{q_s(K^a + 2K^b c)c}{(1 + K^a c + K^b c^2))} \tag{13.14}$$

where K^a and K^b are isotherm coefficients. If both the K^a and the K^b are positive then q_s represents half of the saturation capacity of the stationary phase.

4. BET (Brunauer–Emmet–Teller) isotherm. It is an extension of the Langmuir isotherm for the multilayer attachment of the molecules over the stationary phase, assuming monolayer attachments of solutes on the solute layers that have already been attached whose number approaches infinity. It can be observed from Figure 13.5c that the solute attachment behavior resembles the attachment expressed by Langmuir isotherm at lower solute concentrations. For higher solute concentrations, however, it goes via an inflection point and behaves more like an anti-Langmuir isotherm. The formulation of this isotherm is:

$$q^0(c) = \frac{q_s K^a c}{(1 - K^b c)(1 - K^b c + K^a c)} \tag{13.15}$$

where K^a is the equilibrium constant for the solute attachment on the bare stationary phase surface, whereas K^b is the same for the solute attachment on the layers of already attached solute and therefore typically $K^a > K^b$. For the BET isotherm the fluid phase concentration has an upper bound and cannot exceed the value of $1/K^b$. It can be noted from the formulation of BET isotherm that the Langmuir and the anti-Langmuir isotherms are its special cases. BET becomes Langmuir when $K^b = 0$ and $K = K^a$, that is in the absence of any multilayer solute attachment, and anti-Langmuir when $K^a = K^b = K$, which means the interaction of the first layer of molecules with the bare surface is as strong as between the layers of attached solute molecules.

5. Linear isotherm. Although a linear isotherm does not occur under any types or classifications, it is important for understanding the other isotherms. This is actually the simplest equilibrium relationship between the mobile and the stationary phase concentrations of a component and is valid at extremely diluted concentrations of the mixture components. It can be written as:

$$q^0(c) = q_s K c = Hc \tag{13.16}$$

Here H is called the Henry's coefficient or Henry's constant, which is numerically equal to $q_s K$. It can be noted that all the other isotherms described here can be approximated by the linear isotherm when $c \longrightarrow 0$. In other words, the factor $q_s K$, which appears in all the so-called nonlinear isotherms can be estimated from the simpler relationship between q and c, which exists at extremely low concentrations of the mixture components.

It can be noted here that determination of the isotherm of a single component is only a part of the whole isotherm determination processes. The main job is to determine the multicomponent isotherm, or the binary isotherm in case of binary separation. When two components of a mixture are eluting together in a column their interactions with the stationary phase can be significantly influenced by each other, especially at higher concentrations. Single component isotherms, which measure the independent interactions of individual components, are not useful for modeling such interactions. The direct measurement of binary isotherms through the experimental route can be significantly challenging and is rarely conducted. Developing binary isotherm models by studying the chromatographic

behavior of the component molecules can also be quite daunting, especially with nonstandard solute attachment behavior [9]. A convenient approach in this direction is to employ the IAS theory to determine the binary isotherms based on the parameters measured from pure component isotherms. A list of the binary isotherms developed through IAS theory can be found from the literature [2, 8]. In the current context, only a Langmuir–Langmuir binary isotherm is presented, which can be written as:

$$q_i^0(c_i) = \frac{q_{s,i} K_i c_i}{1 + K_1 c_1 + K_2 c_2} \tag{13.17}$$

13.5.3 Experimental Steps to Generate First Approximation

In this subsection a set of experiments will be described whose results can be used to generate the first set of estimates of the isotherm and the transport parameters. The experiments are to be conducted in analytical chromatographic columns using the same stationery phase and solvent that will ultimately be used in the actual separation process. Typical sizes of these analytical columns could be 0.46 cm diameter and 15 or 25 cm length. It can be noted from the equations described above that the total number of parameters to be estimated here are four per component when either the Langmuir or the anti-Langmuir isotherm is used. The figure becomes five when either the Quadratic or the BET is used.

Based on the compounds and the feed-solution concentrations, the experiments can be broadly divided into three groups:

(a) experiments with infinitely diluted solution of a molecule which is not attracted to the stationary phase, for example theo-urea, also called a tracer;
(b) experiments with infinitely diluted solution of the mixture components;
(c) experiments with concentrated solution of the mixture components.

13.5.3.1 Information Obtainable from the Tracer Injection Profile

Estimation of void fraction (ϵ)

Estimation of the void fraction (ϵ) inside a chromatographic column is a necessary step for estimating the other parameters. In the absence of any absolute scale, the retention properties of the mixture compounds are measured relative to the retention of a *tracer* molecule, whose flow path inside the column is not influenced by any attraction towards the stationary phase. A common compound used for this purpose is theo-urea.

To conduct this experiment, first inject a small pulse (1 μL) of theo-urea, pump the mobile phase through the column and record the elution time of the tracer. From the recorded elution profile, note the tracer retention time (t_0, note Figure 13.6) which is the elution time of the highest concentration. Then, from this retention time, calculate the total void fraction as:

$$\epsilon = \frac{Q t_0}{V_c} \tag{13.18}$$

where, Q = the volumetric flow rate (mL/min), V_c = the column volume (mL).

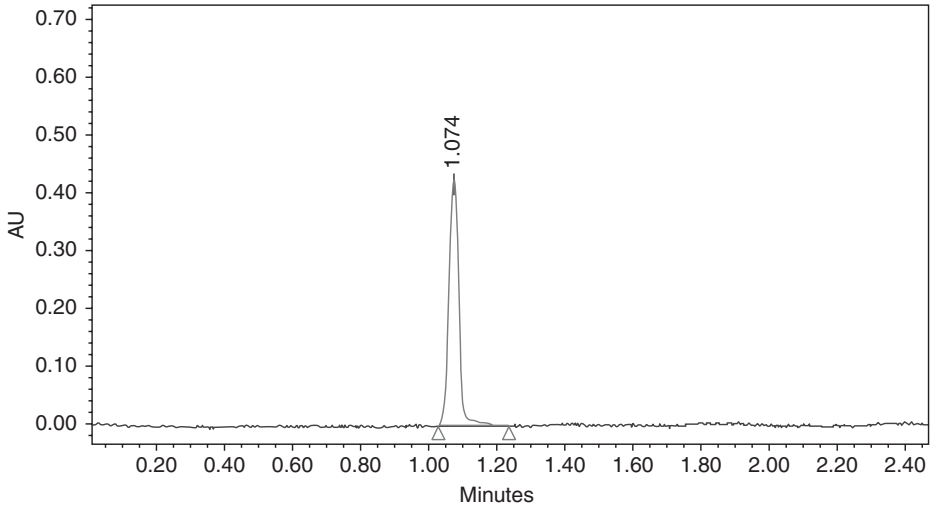

Figure 13.6 *Example of a tracer profile showing the elution time of the component.*

13.5.3.2 Information Obtainable from Experiments with Infinitely Diluted Sample Solution

Estimation of the Henry's Constant

Estimation of the Henry's constant of each of the mixture components is an important step towards model characterization. Although carried out in very dilute conditions, the results from the experiment can provide a near accurate estimation of the Henry's constant, which is a product of q_s and K.

To carry out the experiments, first send a small pulse (1 μL) of an infinitely dilute solution of the mixture through the column and record the elution profile. From the retention times of the bands of the components, ($t_{R,i}$), and the values of t_0 and ϵ, obtained in the previous step, the Henry's constant of component i can be calculated as:

$$H_i = \left(\frac{\epsilon}{1-\epsilon}\right)\left(\frac{t_{R,i} - t_0}{t_0}\right) \tag{13.19}$$

where ($t_{R,i}$) can be determined either directly from the elution time of the individual peaks of the components, as was done for the tracer, or, from the moment analysis as [2]:

$$t_{R,i} = \mu_i = \frac{\sum_{j=1}^{n} c_{i,j} t_{i,j} \Delta t_{i,j}}{\sum_{j=1}^{n} c_{i,j} \Delta t_{i,j}} \tag{13.20}$$

where, μ_i is the first moment of the data, and $t_{i,j}$ and $c_{i,j}$ represent the j^{th} elements of the t and c_i vectors, representing the elution profile of component i. $\Delta t_{i,j}$ represents the time differential, which can be expressed as $\Delta t_{i,j} = t_{i,j+1} - t_{i,j}$.

In ideal conditions the band profiles of individual components will be gaussian and the moment analysis result should replicate the time of highest concentration elution. If on the other hand the band elutes with some deformation, the moment analysis method is more accurate.

In some chromatographic operations the mobile phase composition is varied during the operation, leading to changing thermodynamic interactions inside the chromatographic system. In such conditions Henry's constant cannot be used for modeling, rather the H_i should be expressed as a function of the solvent composition. A convenient way to accomplish that is to measure the H_i, following the procedure discussed above, at different solvent compositions and correlate the solvent composition versus H_i plots with a suitable equation.

Estimation of the Transport Properties

Estimation of the transport parameters used in the LK model, $D_{a,i}$ and $k_{m,i}$, can be conducted with a similar set of experiments. To calculate the transport properties, the experiment described above should be carried out at least two more times, with different solvent-flow rates and their elution profiles recorded. From the recorded profiles, the first and the second moments are to be calculated. The first moments can be calculated using the same expression as described above (Equation 13.20). The second moment can be calculated from the same set of data ($t_{i,j}$ and $c_{i,j}$) and the calculated first moments in the following way:

$$\sigma_i^2 = \frac{\sum_{j=1}^{n} c_{i,j}(t_{i,j} - \mu_i)^2 \Delta t_{i,j}}{\sum_{j=1}^{n} c_{i,j} \Delta t_{i,j}} \tag{13.21}$$

where all the variables are the same as defined above. After calculating the first and the second moments for all the experimental profiles, the height equivalent to the theoretical plates or the HETP of the column can be calculated for each component as:

$$HETP_i = \frac{\sigma_i^2}{\mu_i^2} L \tag{13.22}$$

where L = column length.

The motivation for calculating the first and the second moment of the experimental profiles is to calculate the HETP corresponding to a particular component. If the method looks complicated, HETP can be also calculated directly from the experimental band profiles by noting the retention time and the peak width at half the concentration of the maximum concentration. The HETP can be calculated using a simple relationship, given as:

$$HETP_{k,j} = \frac{L}{N_{k,j}} N_{k,j} = 5.545 \left(\frac{t_{R,i}}{w_{1/2,i}} \right)^2 \tag{13.23}$$

Figure 13.7 shows how the value of $w_{1/2,i}$ can be calculated from a band profile.

After calculating the HETP for all the three (or more) different experiments using different flow rates of the mobile phase, the HETP values are plotted w.r.t. the superficial velocity ($u_k = Q_k/A$) of the mobile phase. The variable k represents the experiment number. A suitable choice of flow rates could be 1, 1.5 and 2 mL/min of the mobile phase. All the HETP points calculated with different velocities should fit into a linear equation, which can be expressed as $HETP_i = C_{1,i} + C_{2,i}u$. The values of the coefficients $C_{1,i}$ and $C_{2,i}$ can be calculated from the plot.

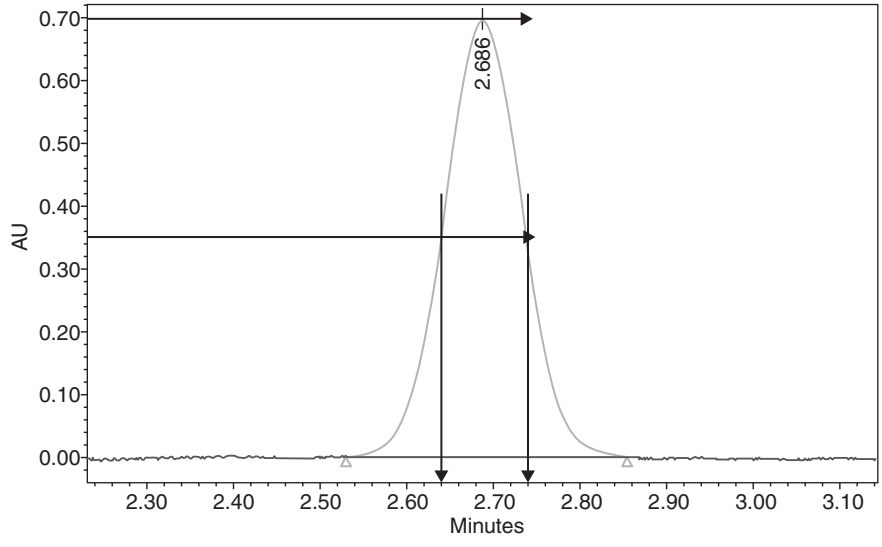

Figure 13.7 *Example of calculating the peak width at the half of the height. Note that from the highest signal the half height is first noted (here the highest signal is 0.7 so the half height is 0.35). Then the peak width is calculated by dropping perpendiculars on the time axis from the half height points. In this example the* $w_{1/2,i} = 0.1$ *min.*

Now to relate these values calculated from the experimental profiles we can use a formulation developed by van Deemter *et al.* [10], which expresses HETP as a function of superficial velocity as:

$$HETP_i = 2\frac{D_{a,i}}{u} + \frac{\epsilon}{1-\epsilon}\frac{2u}{H_i k_{m,i}}\left(\frac{(1-\epsilon)H_i}{\epsilon + (1-\epsilon)H_i}\right)^2 \tag{13.24}$$

Let us assume $D_{eff,i}$ as a function of $D_{a,i}$ as:

$$D_{eff,i} = \frac{D_{a,i}}{u} \tag{13.25}$$

which basically transforms Equation 13.24 into:

$$HETP_i = 2D_{eff,i} + \frac{\epsilon}{1-\epsilon}\frac{2u}{H_i k_{m,i}}\left(\frac{(1-\epsilon)H_i}{\epsilon + (1-\epsilon)H_i}\right)^2 \tag{13.26}$$

From the fitted coefficient values obtained from the experimental results, the transport properties $D_{a,i}$ and $k_{m,i}$ can be calculated as:

$$D_{a,i} = \frac{C_{1,i}}{2}uk_{m,i} = \frac{\epsilon}{1-\epsilon}\frac{2}{H_i C_{2,i}}\left(\frac{(1-\epsilon)H_i}{\epsilon + (1-\epsilon)H_i}\right)^2 \tag{13.27}$$

If the ED model is used, where all the column inefficiency is attributed to a single parameter, $D_a x$, experiment with a single flow rate is sufficient, where $D_{a,i}$ is calculated as:

$$D_{a,i} = \frac{HETP_i}{2} u \tag{13.28}$$

In summary, in this section, the first estimate of the Henry's constant (H_i) and the transport parameters ($D_{a,i}$ and $k_{m,i}$) was calculated from band profiles of the mixture components injected as a very dilute solution.

13.5.3.3 Information Obtainable from Experiments with Concentrated Sample Solution

Estimation of the Equilibrium Constants

The motivation of this set of experiments is to determine the so-called nonlinear terms in the isotherms described previously. To carry out the experiments, one needs to prepare the sample solution close to the solubility limit. Then send multiple pulse injections, with increasing injection volume (e.g. 5 μL, 20 μL, 50 μL, 150 μL, 250 μL, etc.) and record the elution profiles.

To de-link the process of the determination of the isotherm from that of determination of the isotherm parameters, individual band profiles can be observed by noting the direction of the shift of the maximum concentration, with increasing overloading, as demonstrated in Figure 13.5:

- Langmuir isotherm if with increasing overloading, the peak maximum elutes increasingly earlier.
- Anti-Langmuir isotherm if with increasing overloading, the peak maximum elutes increasingly later.
- BET (Brunauer–Emmet–Teller) isotherm if with increasing overloading, the peak maximum first elutes earlier and after a certain concentration starts eluting later.
- Quadratic or the S-shaped isotherm if the elution behavior is just opposite to the BET isotherm; that is, if the peak maximum eluting later with increasing overloading and after a certain overloading eluting earlier.

After selecting the isotherm following the above criteria, the next step will be to determine the rest of the isotherm parameters. The most straightforward way to do this is to employ the the IM method in two stages. In the first stage all the parameters calculated from the experiments should be kept constant and only the equilibrium constants (K for Langmuir and anti-Langmuir, and K^a *and* K^b for BET and Quadratic) considered as the decision variable, leading to their determination. Simple optimization routines, such as the simplex method, could be used to do this job, which should be fast enough. In the second stage, all the isotherm and the transport parameters should be considered as decision variables for a inverse method analysis. A suitable single-objective optimization method, for example single objective GA from from KANGAL web site, www.iitk.ac.in/kangal/codes/rga/rga.tar (accessed 10 December 2012) can be used for this purpose, designing the decision variable range around the first approximation.

13.6 Description of the Optimization Routine—NSGA-II

The Non-dominated Sorting Genetic Algorithm (NSGA) was developed based on the fundamentals of the genetic algorith, GA [11] for detecting Pareto-optimal solutions while solving multi-objective optimization problems. The GA is a stochastic optimization technique, which works on the principles of genetics and of natural selection. It is a population-based method, which searches for the solution starting with multiple initial estimation points. The GA starts with a set of initial estimates of independent variables or decision variables, which were randomly generated, and tries to find the optimal solution employing special operators such as reproduction, crossover, and mutation. Each iteration is named as a generation where the values of the independent variables are recalculated by applying these operators to the old values.

Nondomination refers to a solution being better in at least one objective compared to another solution in the population. The concept of nondomination, which was first introduced by Goldberg [11], is necessary to assign a fitness value to each solution, which ultimately determines its place in the Pareto-optimal set. Deb and co-workers [12, 13] developed the NSGA based on the theory of nondomination. Elitist NSGA or NSGA-II was developed to improve NSGA. In NSGA-II the computational complexity was significantly reduced, and by applying elitism, which is a method to preserve good solutions, the performance of the algorithm could be increased [6]. Deb *et al.* [6] demonstrated that with NSGA-II one can achieve better convergence near the true Pareto-optimal front and can detect a better spread of solutions. Genetic algorithm operators, which are designed to be applied to binary numbers, require binary coding for the real values of decision variables. Deb *et al.* [13] earlier noted that if one represents the real numbers with binary coding, it leads to a number of problems; for example, the finite-length binary strings were not able to achieve high precision in the decision variables. Additionally, for some string configurations, it needs alteration of many bits to mutate to a neighboring point. This can hinder the gradual search in the continuous search space, a phenomenon also called the Hamming cliff problem. To counter these problems, the simulated binary crossover (SBX) operator and polynomial mutation operator, which are genetic operators capable of operating directly on real numbers, was proposed [13] by Deb and Agrawal, which was used in this study. NSGA-II has been successfully used to solve a variety of multi-objective optimization problems [14–17], where the real-coded NSGA-II, or the NSGA-II using the SBX and polynomial mutation operators, was reported to be performing better than other algorithms. The optimization routine NSGA-II was selected for this study mainly because of its proven prowess in detecting the global optima in stiff problems, like the one offered by the chromatographic process.

13.7 Optimization of a Binary Separation in Chromatography

13.7.1 Selection of the Objective Functions

The main objective of the chromatographic units, like other chemical processes, is to maximize the value addition. The operating costs related to a chromatographic setup mainly come from the use of the solvents and from intermittent replacement of the stationary phase particles. The issue of solvent consumption in chromatography is becoming a major

concern because organic solvents are becoming increasingly costly to procure and also to dispose of. Regarding the stationary phase, the cost of replacement can vary considerably based on the type of materials being used. For example, the stationary phases used in affinity chromatography for protein separation uses special ligands, which make it exorbitantly costly compared to other chromatographic operations, for example using silica as the stationary phase. It is difficult reasonably to take into account the costs of all the different contributions to the chromatographic operation and also the estimated profit made from the separation, so some general objectives can be considered. For example, the general performance of a chromatographic process can be evaluated by different parameters representing various aspects of the efficiency of separation. To maximize the production of a compound we need to produce fast. We should also be careful about the use of the mobile phase and should try to reduce the consumption. We should also try to recover the maximum of the target product, which brings profit. We also have to be careful about the purity of the product, which should meet the quality analysis. All these criteria lead to identifying at least three objectives of the optimization studies: (i) the productivity, which is a count of the efficiency of the production unit and should be maximized, (ii) the solvent consumption, which should be minimized for cost reduction and also for environmental concern, and (iii) the product recovery (or the yield), which should be maximized to increase earnings. The purity, which should be maintained for the effectiveness of the product, is more suitable as a constraint. Mathematically these objective functions can be described as:

$$Productivity = \frac{m_{p,rec}}{t_{sep} V_{col}} \tag{13.29}$$

where, $m_{p,rec}$ is the mass of the target component being recovered, t_{sep} is the time taken by the separation and V_{col} is the volume of the chromatographic column used for this separation.

$$Solvent\ consumption = \frac{t_{sep} Q}{m_{p,rec}} \tag{13.30}$$

where, Q is the volumetric flow rate.

$$Yield = \frac{m_{p,rec}}{m_{p,in}} \tag{13.31}$$

Where, $m_{p,in}$ is the total mass of the target component injected in the system.

13.7.2 Selection of the Decision Variables

The decision variables, or the design variables, related to a chromatographic separation can be numerous. The variables can be broadly classified under the categories of (i) column properties and (ii) operating conditions.

Under column properties we can consider the column dimensions, which are the length and the diameter of the column, and the size of the stationary phase particles. The most prominent contribution of these parameters is on the pressure drop across the column and the also the column efficiency. Longer chromatographic columns provide the system with additional time for separation, resulting in a better yield. This, however, also increases the reduction in pressure across the column, which may not be acceptable beyond certain values. Increasing the diameter, on the other hand, decreases the pressure drop, theoretically without having any effect on the separation performance. In industry, a favourite method

of scaling up is to increase the diameter of the column. Increasing column diameter, however, may reduce long-term bed stability and column efficiency. There are complaints that the efficiency of wide columns decreases sharply after a certain period of satisfactory operation, which can be from a few days to several months. Column dimensions can be an important decision variable during the design of the chromatographic setup. Using smaller particle size in chromatographic columns results in higher efficiency, which means less broadening of chromatographic bands resulting from transport phenomena. This is crucial during the analysis of complex mixtures where inefficient columns can overlap multiple bands, resulting in ineffective analysis. For industrial separation, however, the situation is different. Chromatographic bands are broadened by the nature of solute attachment itself and the effect of transport behavior on band broadening is not that significant. This, however, does not reduce the role of the particle size and one can use this as a design variable.

The decision variables from the operating conditions can be numerous. The main operating conditions in a liquid chromatographic system are the temperature, composition and the flow rate of the mobile phase. The feed conditions—the concentration of the feed solution and the volume of feed injected in the column—can be also important design variables. The temperature and the composition of the mobile phase control the equilibrium behavior of the mixture components between the mobile and the stationary phases and also the solubility of the mixture in the mobile phase. Temperature, however, is rarely considered as a design variable and is kept constant at the ambient temperature. The composition of the mobile phase, on the other hand, is frequently manipulated to design suitable operating conditions for a particular separation and can be used as a decision variable in optimization studies.

Both the feed concentration and the volume of injection defines the throughput of a particular separation run. The feed mixture is generally prepared with the same solvent composition as used in the mobile phase. The feed concentration is limited by the solubility of the mixture in the mobile phase. The total mass of injection is finally determined by the injection volume of the feed solution. Concentrated smaller feed injections are generally preferable but if the solubility is low it may be necessary to increase the feed volume. Both these parameters can be used as decision variables.

13.7.3 Selection of the Constraints

Selection of a constraint will depend mainly on the acceptable range of the objectives. All the objectives discussed earlier can be set as a constraint depending on the values the practitioner is looking for. For example an optimization study can be set where no solutions below a certain productivity or a yield level are acceptable. Similarly there could be a higher limit set for the solvent consumption. The most common constraint applicable during an optimization study of a chromatographic process is purity. The reason for this is that, during production, purity is normally considered as a set criterion that should be achieved. A product in which the purity of the target component is below a required value, is not acceptable and may not be deemed as product at all. Again, a product, whose purity is much higher than the required value, may be considered as a loss of throughput. Such observations show that purity is more suitable as a constraint.

$$Purity = \frac{m_{p,rec}}{m_{t,rec}} \tag{13.32}$$

where, $m_{t,rec}$ is the total mass recovered as a product from the column.

13.8 An Example Study

The main purpose of the current section is to present an example of a multi-objective optimization study of the design of a chromatographic system. The scope of optimization studies for such a system can be vast, as should be evident from the issues discussed in the previous sections. For the current chapter a simple example has been selected for the purpose of demonstration. In the example separation problem, a binary mixture is considered. In the following subsections the scheme of the optimization study will be discussed in detail, and this will be followed by a discussion of the results of the study.

The dimensions of the column selected for the simulation studies have been kept constant, with the following values:

column length = 25 cm, column diameter = 0.46 cm, and column porosity = 0.74

Such columns are generally used in a laboratory setup. The performance of such columns with highly concentrated feeds can closely resemble the performance of larger units, so such columns can be used during the method development period, especially when the mixture to be separated is too costly to be used in abundance in the method development studies. The results obtained from the studies employing such column dimensions can be tested conveniently to ensure the reliability of the optimization study.

13.8.1 Schemes of the Optimization Studies

The characterization of the chromatographic model was based on assumed values as the aim here was to present a simple example of a multi-objective optimization study. The isotherm model chosen for both the components of this binary mixture is the Langmuir model (Equation 13.12), leading to the binary Langmuir isotherm as described in Equation 13.17. The transport parameters chosen for both the components are the same. The axial diffusion coefficients, $D_{a,i}$, are chosen as $0.005 \times u$ (cm^2/min), where u is the mobile phase velocity. The mass transfer coefficient, $k_{m,i}$ for both the components are chosen as $1000(\frac{1}{min})$. The isotherm parameters are considered as decision variables and will be explained later.

The Objectives

The objectives considered here are the yield and the productivity, as described in Equations 13.31 and 13.29 respectively. Both the objectives were set to be maximized. As the real variable NSGA-II requires the objective functions to be described as minimization type, for maximizing the yield and the productivity, the objective functions were inverted following a well tested approach:

$$J_1 = \frac{1}{1 + Yield} \tag{13.33}$$

$$J_2 = \frac{1}{1 + Productivity} \tag{13.34}$$

Solvent consumption, although a very important criterion for an effective design of chromatographic operations, was not considered as a separate objective here because maximizing productivity in a way ensures reduced solvent consumption and may not lead to interesting results, especially for the demonstration purposes.

The Decision Variables

The decision variables chosen for this study were the following:

1. Composition of the mobile phase.

   Composition of the mobile phase can be altered by mixing an organic solvent into another. By changing the composition of the mobile phase, one can alter the thermodynamic interactions of the mixture molecules (whose components are to be separated) with the stationary phase. The solvent that plays the stronger role in defining the properties of the mobile phase is called a modifier. Thermodynamic properties, for example Henry's constant, can then be expressed as functions of the modifier concentration. In the current study a power function has been considered to define Henry's constant as a function of the modifier in the following way:

$$H_i = ac_{mod}^b \tag{13.35}$$

   where c_{mod} is the concentration of the modifier, and a and b are the coefficients of the power function.

   To determine the values of the coefficients, one can measure H_i at different c_{mod} and then correlate the corresponding plot with a power function. In the current study, for the current case, the values of a and b are chosen as $a_1 = 2000$ and $b_1 = -1.2$ for component 1, and $a_2 = 1400$ and $b_2 = -1.3$ for component 2.

   The range of the modifier concentration, which is the first decision variable used for this study, was taken from 100 to 300 g/mL. The choice of this values and also the coefficients a and b, were arbitrary, guided by the criteria that the resulting H_i values should be low enough so that the components are relatively weakly retained, leading to shorter computing time. The variations in Henry's constant, based on the coefficient values and the range of modifier concentration variation are shown in Figure 13.8. At different modifier concentrations the ratio between the Henry's constants of the two

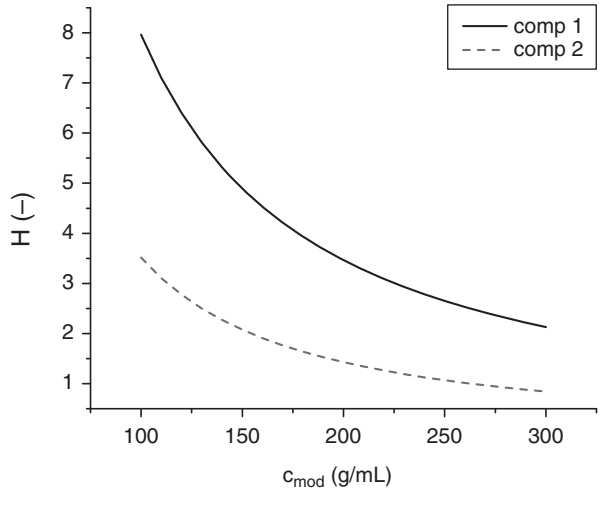

Figure 13.8 *Variation of the Henry's constant of two component molecules with respect to the modifier concentrations.*

components, which is also called the selectivity, are different. At the lowest modifier concentration the selectivity is the highest and it gradually reduces with the modifier concentration. Higher selectivity signifies greater distance between the eluting bands, which is desirable during a separation as it will allow better collection of the purer products. So a higher selectivity should facilitate higher yield and higher purity. This condition, however, also leads to higher residence time of the components in the column, leading to lower productivity.

The remaining parameter of the Langmuir isotherm, the equilibrium constant, was determined based on the values of the Henry's constants following the formulation:

$$K_i = \frac{0.1}{H_i} \tag{13.36}$$

Note that by selecting the modifier concentration as a decision variable we are trying to evaluate different mobile phase concentrations that will be suitable for this separation. Once a certain concentration is selected for evaluation, it is kept constant in the separation. So in the current study we are not allowing the modifier concentration to change during the operation; rather, we are providing the optimizer the option to select a modifier concentration to conduct a particular run.

2. Concentration of the feed solution.

   The concentration range of the feed solutions chosen for this study is from 1 to 100 g/mL. This choice is arbitrary, the motivation being to provide the optimizer with a vast range of concentrations to select from. In practical situations the upper limit can be chosen from the solubility limit of the mixture in the solution.

3. Time of injections.

   The range of injection time selected for this optimization study is from 0 to 1 min. Injection time coupled with the flow rate of the mobile phase defines the total volume of feed. The volume of feed coupled with the concentration of the feed solution defines the total mass of the mixture, which is being fed into the column. Although the total mass injected could have been considered as a single objective, the motivation behind distributing this factor into three different factors is (i) to mimic the real situation, and (ii) provide more options to the optimizer to test with.

4. Mobile phase flow rate.

   The range of flow rates used here is from 1 to 5 mL/min. The selection of these values are mainly based on experience. In particular, the upper limits were selected at the very high range of operability of such type of columns.

The Constraints

The constraint chosen for this study was purity, as defined in Equation 13.32. Three different studies were conducted, taking an equality constraint of purities of 99%, 98% and 95%. Equality constraints are always difficult to handle for the optimization studies, but in this study an equality constraint on the purity could be imposed without explicitly declaring it as a constraint. This was done following a simple scheme which can be described more clearly with the help of Figure 13.9. In Figure 13.9, the times $t_{c,s}$ and $t_{c,e}$ indicate the starting and the end time of the cycle; the times $t_{p,s}$ and $t_{p,e}$, on the other hand, indicate the starting and the end time of the collection of the product. If the target compound here is the compound eluting earlier, the starting point of product collection can coincide with

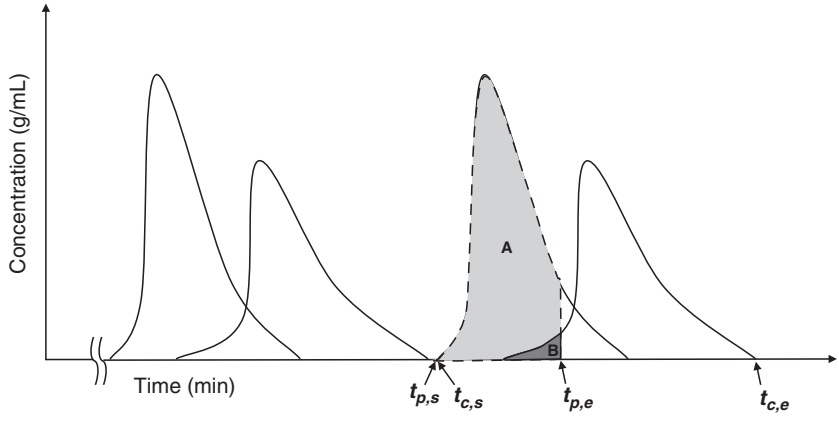

Figure 13.9 *Schemes for calculating the purity, the yield and the cycle times from the elution profiles. The times $t_{c,s}$ and $t_{c,e}$ indicate the starting and the end time of the cycle. The times $t_{p,s}$ and $t_{p,e}$, on the other hand, indicate the starting and the end time for the collection of the product.*

the starting point of the cycle, which is shown in Figure 13.9. To calculate the end time of the product collection, $t_{p,e}$, the elution profile data needs to be analyzed, converting the time versus concentration vector into a time versus total mass elution vector. This gives the exact time until which the product should be collected to reach a redefined purity. This is illustrated in Figure 13.9, which shows that to ensure a purity of x (say) we need to collect the product until the time when the ratio of $\frac{A}{A+B} = x$. So the purity constraint actually determines the collection time $t_{p,e}$ here, and this is used to calculate the product yield.

Note that the cycle time is not calculated as the entire time the mixture components stayed inside the column, rather it is calculated as the time taken by the components to elute. This was done with the assumption that for increased utilization of the stationary phase, one can conduct multiple injections into the column so that trains of separated compounds can be processed inside the system, as shown in Figure 13.9.

13.8.2 Results and Discussion

The Pareto-optimal solutions generated by this simple study are shown in Figure 13.10. It can be noted from the figure that the Pareto fronts are quite well defined and well formed, demonstrating the optimum tradeoff between the yield and the productivity. The maximum possible yield of 1.0 could be achieved with all the purity constraints, although a higher purity requirement resulted into drops in productivity near yield = 1.0. As expected, relaxation in purity requirements resulted in higher productivity against all the yields. Although the numerical values of yield and productivity do not mean much, we still can deduce some general conclusions from the trend in the variation of the results. For example, it can be noted from Figure 13.10 that the maximum gain in productivity is achieved by trading off with the yield until yield $\simeq$ 0.9. After that, the gain in productivity is not significant even after sacrificing the yield to a considerable extent. This general observation is mostly valid for all the three cases of purity constraint.

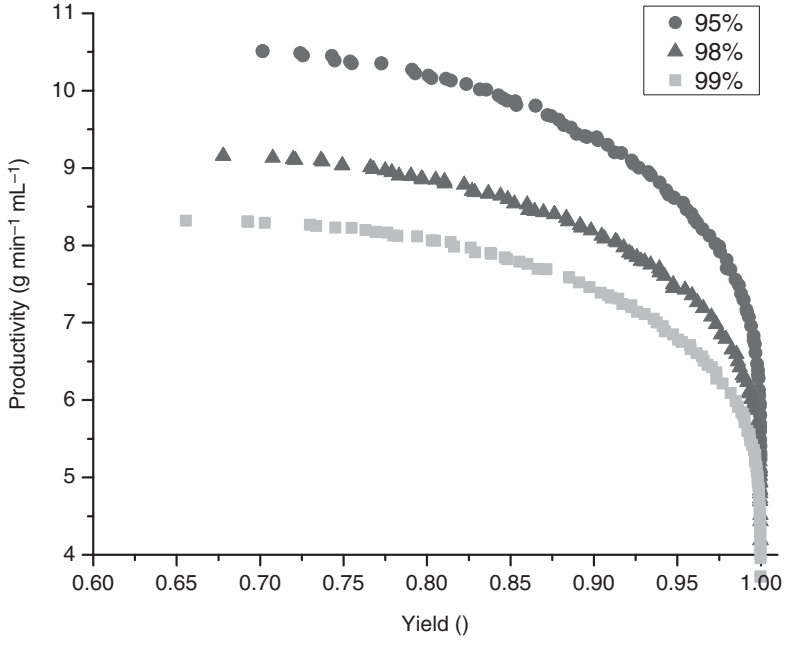

Figure 13.10 *Pareto optimal solutions for Case 1 with purity constraints of 95%, 98% and 99%.*

Let us now analyse the results of the decision variables for all these studies. The results for all the three purity constraints are plotted in the same figures for individual decision variables, as shown in Figure 13.11. From the plots it can be noted that for all the three constraints the lowest modifier concentration, which is 100 g/mL, was chosen. This shows that in all the situations the best option was to go for the highest selectivity, despite having higher residence time of the components in the column. Although the H_i versus modifier concentration relationship was formed purely on a theoretical basis, a general observation that can be noted from the results is that higher selectivity is definitely a better option during separation, especially while trying to maximize productivity.

A comparison of the values of the feed concentrations between the three purity constraint cases illustrate the reason behind the achievement of higher productivity with a greater relaxation in the purity requirement. For the 95% purity requirement, the system could handle a higher feed concentration, hence higher mass input, while maintaining the same/similar yield. Evidently, higher feed concentration led to higher productivity. To demonstrate how this happened, three different elution profiles from the three constraint studies are plotted together in Figure 13.12. In all the cases, the resultant yield was 80%. To maintain increasingly higher purity, the optimizer had to select a decreasing injection of mass, which it did by lowering the feed concentration, leading to lower productivity.

A comparison of the flow rates shows that the upper limit of the range was always chosen by the optimizer. A general discussion on the decision variables will be useful to understand the optimization process better. Comparing the decision variables of modifier concentration and flow rates, we can understand that the optimizer could select the lowest

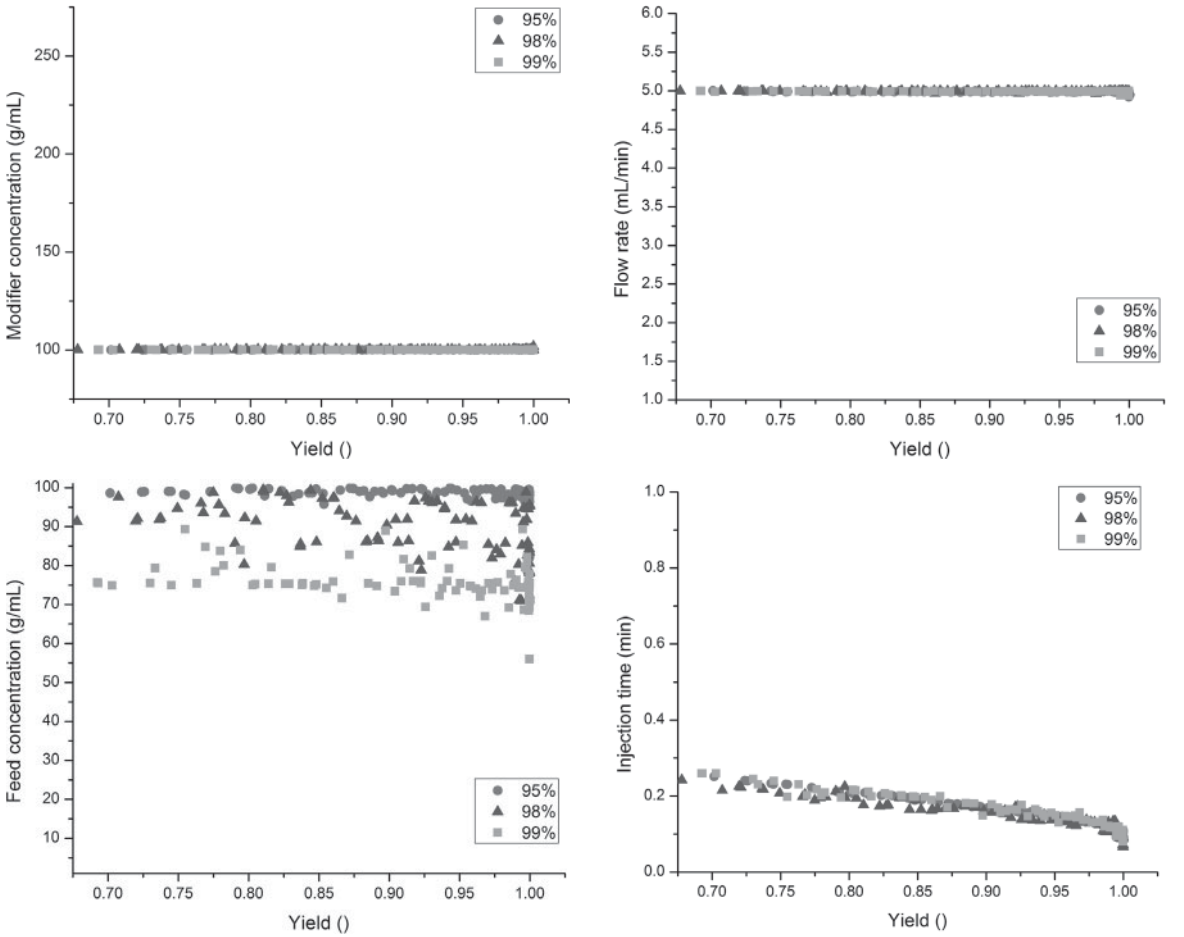

Figure 13.11 *Results for all the three purity constraints plotted together for individual decision variables.*

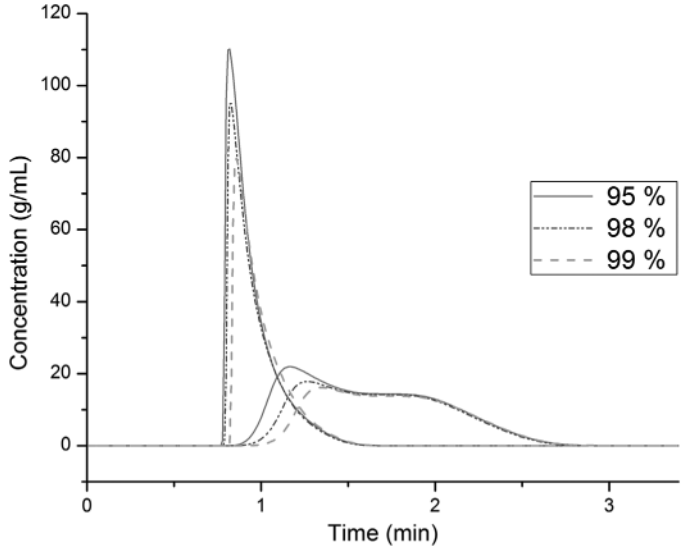

Figure 13.12 *Chromatographic elution profiles of the two components under 95%, 98% and 99% purity constraints. It can be noted from the profiles that with higher purity constraints the optimizer had to select lower mass input.*

modifier concentration to ensure highest selectivity without compromising the productivity, because the highest flow rates could be used. It may be useful to mention here that the upper limit of the flow rate used in this study, which is 5 mL/min, is a bit higher than the practical limit. Using columns with particle sizes like 5 μm, the pressure drop would be substantial and may prevent practical operation. But even if we had considered that criterion and settled for a lower upper limit of the flow rate, the highest flow rate would have been chosen to maximize productivity.

The values of the injection times indicate that this is the decision variable that the optimizer manipulated more selectively to generate the Pareto. For all the three cases of different constraints, the injection times decrease gradually to ensure higher yield of the product, trading off against productivity. As discussed earlier, the injection time along with the flow rate and the feed concentration defines the net mass injected, which strongly influences productivity. From the results it may be concluded that one of the best ways to vary the net mass input is to vary the injection time while keeping the other two variables at the maximum possible limit. In fact, this is a convenient option from the operational point of view too. While designing a change in the operational parameters to move to a new set of objectives, the injection time is the most convenient parameter that one can change.

13.9 Conclusions

Chromatography is a versatile separation technique that can be used for the separation of mixtures which are difficult to separate by other means. Naturally, the products of

a chromatographic separation often fetch very high values. Multi-objective optimization studies, which are useful to bring out the best process conditions, can be employed here, as even minor improvement in the process can result in a significant economic dividend. In this chapter, a dynamic model related to general chromatographic behavior was first described, along with a possible route of numerically solving the related partial differential equations. In the next section various steps for characterizing the general chromatographic model for a particular separation problem were described with examples. Variables typically used as the objectives, the constraints and the decision variables in a chromatographic process were then discussed in detail. Finally, in the results and discussion section, the optimum tradeoffs between the objectives—(i) yield and (ii) productivity—were calculated and described for different purity constraints. Overall, the chapter demonstrates the effticacy of employing a multi-objective optimization study in the design of a chromatographic process.

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