Doctoral Thesis

Simulated moving bed technology for continuous chromatographic reactions and separations

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SIMULATED MOVING BED TECHNOLOGY FOR CONTINUOUS CHROMATOGRAPHIC REACTIONS AND SEPARATIONS

A dissertation submitted to the

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presented by

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2000
Foreword

First of all, I have to acknowledge ETH and Hoffmann-La Roche for supporting my work. But above all I have to acknowledge their support for giving me the possibility to know this wonderful country and Zürich. A major contribution to the understanding of the so called "Swiss-style" (Ski-weekends, clausabend, street parade,...) comes from my friends at IVUK, which provided the best environment not only to work but also to relax and forget the sometimes unsuccessful outcomes of research. In particular, I have to thank Emilio Trigoso for the long discussions, the merende and for helping me in a very difficult moment: grazie!

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Last but not least (!) Simone, Giuseppe and Maria are the most wonderful family and I am the luckiest to have them in my life.

Zürich, April 6th 2000
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Publications


10. Migliorini, C., Meissner, J. P., Mazzotti, M., Carta, G., *Regioselective enzymatic diol esterification in batch and fixed bed adsorptive reactors: experiments and modeling*, Biotechnology progress, in press


Contributions to congresses


11. Migliorini, C., Mazzotti, M., Morbidelli, M., *Robust design of simulated moving bed separations of non-constant selectivity mixtures*, AIChE annual meeting 1999, Dallas, paper 28e
Abstract

Continuous chromatographic separation processes based on the Simulated Moving Bed technology have been gaining greater and greater interest since the beginning of the '90s for applications in the fine chemical and pharmaceutical industries, in particular for the resolution of enantiomers. These are small-scale applications that are carried out in a simple apparatus constituted of standard chromatographic devices, i.e., HPLC columns, chromatographic valves and volumetric pumps. The stationary phases adopted, in particular for enatiom Particles, are the same used for analytical HPLC columns, with small average particle size and high column efficiency. The demand of optically pure compounds and the increasing trend towards restricting the use of racemate drugs require the development of preparative-scale technologies for the separation of enantiomers. In this frame continuous chromatography through the Simulated Moving Bed (SMB) technology has provided one of the most convenient solutions for numerous applications in pharmaceutical and fine chemical industries (food, cosmetics, etc.). This interest has motivated a great deal of experimental and theoretical work to achieve a better understanding of the behaviour of SMBs and to devise useful tools for design and process development purposes. This dissertation focuses on the following points:

- application of the Equilibrium Theory approach for the design of robust operating conditions for new fine chemical separations when systems of with non-constant selectivity are considered (Extension of the triangle theory from Langmuir to bi-Langmuir IAS and RAS isotherms)
- study of effect the extracolumn dead volume on the performances of small scale SMB units
- analysis of non-ideal effects, i.e. finite mass transfer rate, axial dispersion and extra-column band broadening
- experimental short-cut design of new chiral SMB separations

Beside classical separation applications, the SMB technology has been also proposed for hybrid processes, where chromatographic separation and chemical reaction take place in the same unit thus allowing to carry equilibrium limited reactions beyond equilibrium conversion. With reference to these applications, the goal of this work is to develop a detailed model of Simulated Moving Bed reactors (SMBR) and to extend the triangle theory approach as far as possible. Two model systems representative of a large class of applications are studied and optimization with the triangle theory is discussed.
Riassunto

I processi di separazione cromatografica continua con la tecnologia a letto mobile simulato (SMB) hanno acquisito una sempre piu' grande importanza dall'inizio degli anni '90 per applicazioni nell'industria farmaceutica e di chimica fine, in particolare per la separazione degli enantiomeri. Queste applicazioni di piccola scala vengono condotte in apparecchi semplici costituiti da normali colonne HPLC, valvole e pompe volumetriche. Le fasi stazionarie usate, in particolare per separazione di enantiomeri sono le stesse usate per colonne HPLC ad uso analitico, caratterizzate da particelle di piccolo diametro ed elevata efficienza di separazione. La forte richiesta di composti otticamente attivi e la crescente tendenza a restinguere l'uso di principi attivi racemi richiedono lo sviluppo di tecnologie preprarative per la separazione di enantiomeri. In questo contesto, la cromatografia continua a letto mobile simulato fornisce una delle piu' convenienti soluzioni per le numerose applicazioni nell'industria farmaceutica e di chimica fine (industria alimentare, cosmetici,...). Questo interesse ha promosso una grande quantita' di ricerca sperimentale e teorica per raggiungere una migliore comprensione del funzionamento dell'SMB e per trovare strumenti per la progettazione e lo sviluppo del processo. Questa dissertazione si concentra sui seguenti punti:

- applicazione della teoria dell'equilibrio (equilibrium theory) per la progettazione di condizioni operative robuste per nuove separazioni in sistemi a selettivita' non costante (estensione della teoria dell'equilibrio dall'isoterma Langmuir alle isoterme bi-Langmuir e IAS)
- studio dell'effetto del volume morto tra le colonne sulle prestazioni di SMB di piccola scala
- analisi degli effetti non ideali, cioe' velocita' finita del trasporto materiale, dispersione assiale e dispersione nei volumi morti
- procedura semplificata per la progettazione di nuove separazioni chirali con SMB

La tecnologia SMB e' stata proposta, oltre che per le classiche applicazioni in separazione, anche per processi ibridi, dove la separazione cromatografica e la reazione chimica avvengono nello stesso apparato permettendo di raggiungere completa conversione anche per reazioni la cui conversione e' limitata dall'equilibrio chimico. L'obiettivo di questa parte del lavoro e' di sviluppare un modello di reattore SMB e criteri di progetto applicando l'approccio della teoria dell'equilibrio. Due sistemi modello che rappresentano una vasta gamma di applicazioni sono studiati e l'ottimizzazione del processo con la teoria dell'equilibrio e' discussa.
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Chapter 1

SMB Technology

1.1 Background and motivation

Continuous large-scale chromatographic separations using the Simulated Moving Bed (SMB) technology\(^1\) are well-known processes in the petrochemical and food industries, and are now extended to pharmaceutical, fine chemical and biological separations.\(^2\)\(^{-16}\) In particular the separation of enantiomeric mixtures on chiral stationary phases has received recently a great interest due to its potential in achieving high performances and in reducing the time from discovery to production of new products. The development of new separations and the need to optimize their performances motivate the study of SMB process. The research efforts are directed toward the application of this technology to fine chemical separations and toward the development of new applications, such as the gas\(^{17}\) and supercritical phase operation\(^{18}\) and the SMB reactor.\(^{19} -^{25}\)

The SMB technique involves the simulated countercurrent contact between the mobile fluid phase and the stationary phase, which is most efficient in terms of separation performance, eluent consumption and productivity per unit mass of stationary phase. This can be accomplished in units constituted of a set of fixed bed chromatographic columns like that illustrated in Figure 1.1, through the periodic movement of inlet and outlet ports in the same direction of the fluid flow. With reference to a binary mixture to be separated, which constitutes the Feed stream to the unit, the more adsorbable component, called A, is collected in the Extract stream, whereas the less adsorbable one, called B, is collected in the Raffinate stream. Each section of the unit plays a specific role in the operation. The separation is performed in the two central sections, where component B is carried by the mobile phase while on the other hand component A is retained by the stationary phase. The eluent,
indicated as D, is used to desorb component A from the first section, so as to regenerate the adsorbent. Finally, component B is adsorbed in the fourth section of the unit, so as to regenerate the desorbent itself. In order to run continuous operations and to avoid the troublesome movement of the solid phase, the solid movement is simulated by periodically shifting the position of the inlet and outlet ports in the direction of the fluid flow, as shown in Figure 1.1.

![Figure 1.1: Simulated Moving Bed for the separation of A and B. Column layout: 2-2-2-2.](image)

The SMB can be used as a unit operation to carry out separations and reactions, as shown in Figure 1.2. In fact, in reactions limited by chemical equilibrium where more than one product is formed, conversion can be enhanced in a hybrid apparatus where the products are separated as they are formed. The advantages of coupling chemical reaction and separation have been exploited since a long time in the petrochemical industry with reactive distillation processes. In the '60 the integration of chemical or biochemical reactions in chromatographic separation processes has been patented. Recently, with reference to esterification reactions, it has been shown that cation exchange resins can act both as selective adsorbent and heterogeneous catalyst. As a result reactions may be driven to complete conversion and no catalyst has to be removed from the products.
1.2 Objectives

The SMB technology constitutes a rather complex unit operation, which requires a deep understanding in order to make its use effective. To achieve this objective a rather natural approach would involve the use of a general model aimed at performing a parametric analysis of the SMB behavior. Actually, this approach was followed in earlier studies and it is still applied to analyze different aspects of SMB performances. However, comprehensive simulation-based analyses such as the one carried out by Zhong and Guiochon highlight a rather broad range of effects due to the many parameters involved but do not provide a deep understanding of SMB behavior. To this aim a more synthetic view of the process is required. This is actually offered by the model based on the Equilibrium Theory, where mass transfer resistance and axial dispersion are neglected. Applying this model to SMB units under the assumption of Langmuir-type adsorption isotherm yields the so called “Triangle Theory”, which allows to determine optimal and robust operating conditions of SMBs to achieve the required separation specifications.

The details of the principles of Simulated Moving Bed (SMB) units (see Figure 1.1) can be found in many previous works. The key idea is to simulate in the SMB the solid phase motion of the corresponding True Counter Current (TCC) unit by periodically switching the inlet and outlet ports of the unit in the same direction of the fluid flow (with period $t^*$).

Figure 1.2: Scheme of a Simulated Moving Bed (SMBR). Complete conversion and separation can be achieved. The stationary phase acts both as selective adsorbent and catalyst.
The following set of relationships establishes the operating parameters of TCC and SMB units which allow to achieve the same separation performances (see the notation section for the meaning of the symbols):

\[ Q_j^{SMB} = Q_j^{TCC} + Q_S \frac{\varepsilon_b}{1 - \varepsilon_b} \]  
\[ Q_S = (1 - \varepsilon_b) \frac{V}{t_s} \]

Based on these the cyclic steady state of an SMB unit can be studied by considering the steady state of the equivalent four section TCC unit illustrated in Figure 1.3.

![Figure 1.3: Scheme of a True Counter Current Unit (TCC). When the equivalence relationships are satisfied, the steady state performance of the TCC and the SMB performance averaged over a cycle are the same.](image)

In previous works the optimal operating conditions for a True Counter Current adsorptive separation unit (TCC) have been found through the application of Equilibrium Theory, i.e. neglecting axial dispersion and mass transfer resistance. A summary of these results is given in the remaining part of this chapter to make the reader familiar with "Triangle theory". In spite of the mathematical complexity of the problem, the solution can be given through simple relationships, that constrain the dimensionless parameters \(m_j\), defined as the ratio of fluid to solid flow rates in each section of the unit. This leads to the partitioning of the \((m_2, m_3)\) plane, i.e. the operating parameter plane spanned by the
flow rate ratios in the two key sections of the unit, into several regions corresponding to all possible separation regimes: both raffinate and extract are pure; either one of them but not the other is pure; neither is pure. This approach, which is often referred to as the "Triangle theory" for the characteristic shape of the complete separation region (i.e., where both raffinate and extract are pure), has been validated by comparison with experimental data and applied to investigate various separations. The Triangle theory provides a clear picture of the different separation regions in the operating parameter space, which is somehow universal since it depends only on thermodynamics of adsorption but neither on size of the unit nor on productivity and flow rates.

The aim of this thesis is to apply the "Triangle theory" approach to investigate new SMB separations and to devise strategies for SMBR design and optimization. The "Triangle theory" approach has been so far limited systems exhibiting a constant selectivity adsorption behavior described with a Langmuir model. This thesis describes a procedure to design separations exhibiting a non-constant selectivity behavior. This is a case often encountered in the separation of complex chiral molecules. In fact, both the heterogeneity of chiral stationary phases due to the presence of chiral and achiral sites and the nonideal behavior in the adsorbed phase due to the complex interactions between the adsorbates result in a non-constant selectivity adsorption behavior.

The design criteria have been extended first to the empirical bi-Langmuir model (which accounts for the presence of different adsorption sites) and then to the Ideal Adsorbed Solution (IAS) theory model (chapter 2). The results with the bi-Langmuir isotherm show that the non-constant selectivity behavior has a strong impact on the design of operating conditions, in particular close to optimal conditions. The IAS model studies the operating conditions when the two enantiomers have different saturation capacities, as it often happens in applications.

In chapters 3 and 4, the role of non-ideal effects such as extracolumn dead volume and axial dispersion are studied. Although the Equilibrium theory approach of chapter 2 is limited to ideal conditions (infinite column efficiency), it can be applied to study the role of extracolumn dead volumes on the design of the SMB operating conditions. This is a problem related to the scale-down of the SMB process from the Sorbex (tons per year) to the bench scale (grams per day). The prediction of "Triangle theory" is also useful when numerical simulations are carried out. The equilibrium theory region can be seen as the solution of a detailed model when mass transfer is infinitely fast and dispersion is negligible. The simulations confirm the intuitive idea that the finite efficiency separation region lies inside the ideal region. However, they also show that in most cases the ideal separation region
is a good approximation of the region calculated with the detailed model. The results of chapters 3 and 4 are used to interpret successfully experimental results in the literature.

The new design criteria suggest the solution to the problem of designing optimal SMB operating conditions under non-linear conditions without the knowledge of the equilibrium isotherms. A novel experimental design technique is presented in chapter 5 and discussed. The insight gained with the Equilibrium theory solution shows that few column experiments are needed to complete the design procedure. This is of great practical importance in the screening of different methods and in the early stages of a new separation, when detailed information on the adsorption thermodynamics is not available since the amount of pure products is limited.

The second part of the dissertation is focused on reactive chromatography and SMBR technology. If on the one hand SMB technology is well established for chiral and fine chemical separations, the SMBR on the other hand has raised less interest. The SMBR technology holds the promise to improve greatly process performance through process integration. However, the application of this technology is limited mainly by its complexity and by the need to determine a class of promising reactions. To this aim chapters 6 and 7 describe the behavior of two adsorptive chromatographic reactors which have received a lot of attention in the last years. In the first system the catalyst is an enzyme while in the second an ion exchange resin is considered. The models developed take into account both the selective sorption on the adsorbent and reaction and can be used to scale-up the process to the SMB scale, as discussed in chapter 8. In this chapter, the concepts presented in the previous parts are applied to develop a numerical optimization procedure. The simulations provide both a reference for experimental investigation and can be used for an economic evaluation of the process.

### 1.3 Theory: background on the "Triangle Theory"

In the frame of Equilibrium Theory and with reference to Figure 1.3, the dimensionless mass balance equation for the \( i \)-th species in the \( j \)-th section of the TCC unit is given as follows:

\[
\frac{\partial}{\partial \tau} [\varepsilon^* c^j_i + (1 - \varepsilon^*) n^j_i] + (1 - \varepsilon_p) \frac{\partial}{\partial x} (m_j c^j_i - n^j_i) = 0 \tag{1.3}
\]

In the previous equation axial dispersion is neglected, and local equilibrium is assumed according to the relationship:

\[
n^j_i = n^j_i(c) \tag{1.4}
\]
1.3 Theory: background on the "Triangle Theory"

Let us notice that the net flux of the species $i$ in section $j$:

$$ f_i^j = Q_S (1 - \varepsilon_p) (m_i^j c_i^j - n_i^j) \quad (1.5) $$

depends on the dimensionless flow rate ratio parameter:

$$ m_j = \frac{Q_j^{TCC} - \varepsilon_p Q_S}{Q_S (1 - \varepsilon_p)} \quad (1.6) $$

which can be re-written using Eqs (1.1) and (1.2) as:

$$ m_j = \frac{Q_j^{SMB} t^* - V \varepsilon^*}{V (1 - \varepsilon^*)}, \quad (1.7) $$

For a binary mixture in a non adsorbable carrier we will define $A$ and $B$ as the more and less retained component, respectively. The objective is to determine the set of operating conditions which allow to achieve complete separation, i.e. to collect the strong component $A$ pure in the extract and the weak component $B$ pure in the raffinate. To this aim and in order to collect pure product streams and to properly regenerate the eluent in section 4 and the stationary phase in section 1, the following sign conditions for the net fluxes (1.5) must be fulfilled (see Figure 1.3):

- Section 1: $f_A^1 \geq 0$; $f_B^1 \geq 0$ \quad (1.8)
- Section 2: $f_A^2 \leq 0$; $f_B^2 \geq 0$ \quad (1.9)
- Section 3: $f_A^3 \leq 0$; $f_B^3 \geq 0$ \quad (1.10)
- Section 4: $f_A^4 \leq 0$; $f_B^4 \leq 0$ \quad (1.11)

By using Eqs (1.5), these inequalities can be expressed as constraints on the $m_j$ parameters:

- Section 1: $m_1 \geq \frac{n_A^1}{c_A^1}$, $m_1 \geq \frac{n_B^1}{c_B^1}$ \quad (1.12)
- Section 2: $\frac{n_B^2}{c_B^2} \leq m_2 < \frac{n_A^2}{c_A^2}$ \quad (1.13)
- Section 3: $\frac{n_A^3}{c_A^3} \leq m_3 < \frac{n_A^3}{c_A^3}$ \quad (1.14)
- Section 4: $m_4 \leq \frac{n_A^4}{c_A^4}$, $m_4 \leq \frac{n_B^4}{c_B^4}$ \quad (1.15)

It is worth noting that since in the frame of Equilibrium Theory at steady state each section of a countercurrent unit reaches a constant composition profile (or constant state), the superscripts in the equations above indicate the constant state prevailing in each section. In a sense that we will clarify later, such steady state profiles are a function of the operating parameters $m_j$, so that constraints (1.12) to (1.15) are at this stage implicit.
By imposing the constraints (1.12) to (1.15) one can define the region of complete separation in the space spanned by the four coordinates \( m_1, m_2, m_3 \) and \( m_4 \). Except for the case of linear adsorption equilibrium which is trivial, this has been done using the orthogonalization technique mentioned above, which is strictly confined to the use of Langmuir type isotherms including the non-stoichiometric, stoichiometric and the modified Langmuir isotherms. All these isotherms imply constant selectivity, with the only exception of the modified Langmuir isotherm which however can account only for small selectivity variations. This approach can be applied to a much larger class of isotherms including in particular the bi-Langmuir and the multicomponent IAS model which account for large variations of selectivity with composition often encountered in applications.

### 1.3.1 Linear Isotherm

When the feed mixture is infinitely diluted in the components to be separated the competitive Langmuir isotherm approaches the non-competitive linear isotherm

\[
n_i = H_i c_i
\]  

and the constraints on the \( m_j \) parameters of the SMB unit reduce to the following set of decoupled inequalities:

\[
\begin{align*}
H_A &< m_1 < \infty \quad (1.17) \\
H_B &< m_2 < H_A \quad (1.18) \\
H_B &< m_3 < H_A \quad (1.19) \\
\frac{-\varepsilon_p}{1-\varepsilon_p} &< m_4 < H_B \quad (1.20)
\end{align*}
\]

These are the classical constraints for SMB separation under linear conditions. It is worth noting that in the linear case the complete separation region is the square triangle, corresponding to region L in Figure 1.4.

### 1.3.2 Langmuir Isotherm

For the sake of simplicity in this work we deal with the binary Langmuir isotherm:

\[
n_i = \frac{H_i c_i}{1 + K_A c_A + K_B c_B}, \quad (i = A, B)
\]  

where \( n_i \) and \( c_i \) are the adsorbed and fluid phase concentration, respectively; \( H_i \) is the Henry constant of the \( i \)-th component, i.e., the slope of the single component adsorption isotherm.
1.3 Theory: background on the "Triangle Theory"

Figure 1.4: Region of complete separation in the \((m_2, m_3)\) plane under linear conditions. \(W\) is the optimal operating point.

At infinite dilution; \(K_i\) is the equilibrium constant of the \(i\)-th component, which accounts for the competitive and overload effects. Coupling the process requirement of complete separation with the material balances at the nodes of the SMB unit and using the results of Equilibrium Theory for Langmuir systems, yields the following set of conditions that the flow rate ratios have to fulfill in order to achieve complete separation:

\[
H_A < m_1 < \infty, \quad (1.22)
\]

\[
m_{2,cr}(m_2, m_3) < m_2 < m_3 < m_{3,cr}(m_2, m_3), \quad (1.23)
\]

\[
- \frac{\varepsilon_p}{1 - \varepsilon_p} < m_4 < m_{4,cr}(m_2, m_3) = \frac{1}{2} \left\{ H_B + m_3 + K_Bc_B^F(m_3 - m_2) - \sqrt{(H_B + m_3 + K_Bc_B^F(m_3 - m_2))^2 - 4H_Bm_3} \right\}, \quad (1.24)
\]

where the superscript \(F\) indicates feed conditions. The constraints on \(m_1\) and \(m_4\) are explicit. However, the lower bound on \(m_1\) does not depend on the other flow rate ratios, whereas the upper bound on \(m_4\) is an explicit function of the flow rate ratios \(m_2\) and \(m_3\) and of the feed composition.\(^{37}\) The constraints \((1.23)\) on \(m_2\) and \(m_3\) are implicit, but they do not depend on \(m_1\) and \(m_4\). Therefore, they define a unique complete separation region.
in the \((m_2, m_3)\) plane, which is the triangle-shaped region abw drawn in Figure 1.5. The boundaries of this region can be calculated explicitly in terms of the adsorption equilibrium parameters and the feed composition as follows:\(^3\)

- **Straight line \(w_f\):**

  \[
  (H_A - \omega_G(1 + K_{AC}^F))m_2 + K_{AC}^F \omega_G m_3 = \omega_G(H_A - \omega_G) \tag{1.25}
  \]

- **Straight line \(w_b\):**

  \[
  (H_A - H_B(1 + K_{AC}^F))m_2 + K_{AC}^F H_B m_3 = H_B(H_A - H_B) \tag{1.26}
  \]

- **Curve \(r_a\):**

  \[
  m_3 = m_2 + \frac{(\sqrt{H_A - \sqrt{m_2}})^2}{K_{AC}^F} \tag{1.27}
  \]

- **Straight line \(a_b\):**

  \[
  m_3 = m_2 \tag{1.28}
  \]

The coordinates of the intersection points are given by:

- **Point a** \((H_A, H_A)\) \tag{1.29}
- **Point b** \((H_B, H_B)\) \tag{1.30}
- **Point f** \((\omega_G, \omega_G)\) \tag{1.31}
- **Point r** \((\frac{H_B \omega_G [\omega_F (H_A - \omega_G)(H_A - H_B) + H_B \omega_G (H_A - \omega_F)]}{H_A H_B (H_A - \omega_F)}, \frac{H_B \omega_G [\omega_F (H_A - H_B) + H_B (H_B - \omega_F)]}{H_B (H_A - \omega_F)})\) \tag{1.32}
- **Point w** \((\frac{H_B \omega_G [\omega_F (H_A - H_B) + H_B (H_B - \omega_F)]}{H_B (H_A - \omega_F)}, \frac{H_B \omega_G [\omega_F (H_A - \omega_G)(H_A - H_B) + H_B \omega_G (H_A - \omega_F)]}{H_A H_B (H_A - \omega_F)})\) \tag{1.33}

In the above equations \(\omega_F\) and \(\omega_G\) depend on the feed composition; they are the roots of the following quadratic equation, with \(\omega_G > \omega_F > 0\):

\[
(1 + K_{AC}^F + K_{BC}^F) \omega^2 - [H_A(1 + K_{BC}^F) + H_B(1 + K_{AC}^F)] \omega + H_A H_B = 0. \tag{1.34}
\]

As illustrated in Figure 1.5, the complete separation region is surrounded by three regions corresponding to three different operating regimes, i.e., the pure raffinate region, where the raffinate stream is pure but the extract is polluted by component B, the pure extract region, where only the extract is pure but not the raffinate, and the no pure outlet region, where components A and B distribute in both outlet streams.
The information provided by the geometrical representation of the separation regions in the 
\((m_2, m_3)\) plane in Figure 1.5 are correct only if the relevant constraints on \(m_1\) and \(m_4\), i.e., inequalities (1.22) and (1.24), are fulfilled.

It can be seen that the vertex \(W\) of the complete separation region in the plane \((m_2, m_3)\) represents optimal operating conditions in terms of solvent consumption and productivity per unit mass of stationary phase.\(^{37}\) However, by inspection of Figure 1.5 it can also be observed that the slightest disturbance in process conditions, as well as the smallest error in the evaluation of the adsorption equilibrium parameters, may make the operating point leave the optimal location and move outside the complete separation region. This means that the optimal operating conditions are not robust.\(^{33}\) As a consequence, in practical situations the operating point is chosen within the complete separation triangle and not on its vertex, thus reaching a compromise between separation performance, i.e., productivity and solvent requirement, and process robustness.
1.4 Modeling SMB units

1.4.1 Single chromatographic column

The use of several different models for the description of the dynamic behavior of chromatographic columns has been reported in the literature. Models based on the use of the linear driving force approximation are widely applied; despite their simplicity they constitute an accurate tool for the prediction of breakthrough profiles in most situations\(^{52}\). The lumped solid diffusion model is one of these and is constituted of the following set of equations (\(i = A, B\) in the cases of interest here):

\[
\frac{\varepsilon}{\partial t} \frac{\partial c_i}{\partial t} + (1 - \varepsilon) \frac{\partial n_i}{\partial t} + u \frac{\partial c_i}{\partial z} = \varepsilon D_i \frac{\partial^2 c_i}{\partial z^2}
\]  

(1.35)

\[
\frac{\partial n_i}{\partial t} = k_i a_p (n_i^* - n_i)
\]  

(1.36)

\[
n_i^* = f_i^{eq} (c)
\]  

(1.37)

where \(k_i\) is the overall mass transfer coefficient of component \(i\), \(a_p\) is the specific surface of the adsorbent particles and the other symbols are defined in the Notation section. Together with proper initial and Dankwerts boundary conditions these equations can be solved using several different numerical techniques, e.g., orthogonal collocations\(^{53}\) or finite differences\(^{54}\).

It is worth noting that chromatographic column efficiency, i.e., the capacity of the column to minimize band broadening and to achieve good separation performance under analytical conditions, depends on the mass transfer and axial dispersion coefficients, i.e., \(k_i\) and \(D_i\). Column efficiency is often given in terms of number of theoretical stages, \(N_p\).

In the case where the adsorption isotherm is linear, i.e., \(n_i^* = H_i c_i\), then the solid diffusion model (1.35) to (1.36) is equivalent to the equilibrium dispersive model, where mass transfer resistance and axial dispersion are lumped in an apparent axial dispersion coefficient and local equilibrium conditions are enforced:

\[
\frac{\varepsilon}{\partial t} \frac{\partial c_i}{\partial t} + (1 - \varepsilon) \frac{\partial n_i^*}{\partial t} + u \frac{\partial c_i}{\partial z} = \varepsilon D_{ap,i} \frac{\partial^2 c_i}{\partial z^2}
\]  

(1.38)

The equivalence can be achieved as follows. The number of theoretical stages of a chromatographic column described through the lumped solid diffusion model under infinite dilution linear conditions is given by the following relationship:\(^{55}\)

\[
\frac{1}{N_{p,i}^{ad}} = \frac{2D_i \varepsilon}{u L} + \frac{2u}{(1 - \varepsilon) L H_i k_i a_p \left( \frac{(1 - \varepsilon) H_i}{\varepsilon + (1 - \varepsilon) H_i} \right)^2}.
\]  

(1.39)
The efficiency parameter $N_{p,i}^{sol}$ may be different for different solutes, since the controlling parameters, i.e., $k_i$, $D_i$ and $H_i$, are solute specific. The last equation can be recast as follows:

$$\frac{1}{N_{p,i}^{sol}} = \frac{1}{N_{disp,i}} + \frac{2}{N_{mt,i}} \left( \frac{(1-\varepsilon)H_i}{\varepsilon + (1-\varepsilon)H_i} \right)^2.$$  \hspace{1cm} (1.40)

where each dispersive mechanism contributes independently to the overall number of theoretical stages through a number of axial dispersion stages, $N_{disp,i}$, and a number of mass transfer stages, $N_{mt,i}$.

In the case of the equilibrium axial dispersive model (1.38), the number of theoretical stages is given by the following relationship: \cite{55}

$$\frac{1}{N_{p,i}^{read}} = \frac{2D_{ap,i}\varepsilon}{uL}.$$  \hspace{1cm} (1.41)

The last equation can be obtained by Eq. (1.39) by simply letting $k_i$ become infinitely large and substituting $D_i$ with $D_{ap,i}$, thanks to the additivity of the HETP, i.e., the height equivalent to a theoretical plate, expressed by Eqs (1.39) and (1.40). The simplified equilibrium axial dispersive model is equivalent to the solid diffusion model, provided that $D_{ap,i}$ is chosen so that the number of theoretical plates in the two models are the same, i.e., $N_{p,i}^{read} = N_{p,i}^{sol}$ for $i = A, B$.

Under the assumption that the apparent axial dispersion is the same for all components, i.e., $D_{ap,i} = D_{ap}$, the numerical solution of the equilibrium axial dispersive model can be obtained in a computing efficient way by using a finite difference scheme and letting numerical dispersion play the role of the apparent axial dispersion in Eq. (1.38). This is obtained by discretizing the first order space derivative in Eq. (1.38) through backward differences:

$$\frac{c_i(z) - c_i(z - \Delta z)}{\Delta z} = \frac{\partial c_i}{\partial z} \bigg|_z - \frac{\partial^2 c_i}{\partial z^2} \bigg|_z \frac{\Delta z}{2} + O(\Delta z^2),$$  \hspace{1cm} (1.42)

where the neglected terms are proportional to $\Delta z^2$. If the space interval, $\Delta z$, is chosen so that

$$\Delta z = 2\varepsilon D_{ap}/u,$$  \hspace{1cm} (1.43)

then the numerical error, i.e., the second term on the right hand side of Eq. (1.42), corresponds to the axial dispersion term in Eq. (1.38), which is therefore not included in the numerical scheme. It can be observed that using this algorithm the number of grid points, i.e., $N_G = L/\Delta z$, is equal to the number of theoretical stages given by Eq. (1.41).

Mass transfer resistance and axial dispersion effects are often lumped into an apparent axial dispersion coefficient also when the adsorption equilibria (1.37) are nonlinear. However,
this is not rigorous any more and the equivalence between the solid diffusion model and the equilibrium axial dispersive model exploited in the linear case is questionable. One can only say that this equivalence works in many cases of interest, even when the number of stages is rather small, i.e., $N_{p,i} < 100$ (cf. for example56–58). Though fully aware of the degree of approximation introduced by the equilibrium axial dispersive model, in this work we use its version where $D_{ap,A} = D_{ap,B}$ and numerical dispersion is exploited through Eq. (1.43). In fact, this approach allows fast computations and makes it possible to use a single parameter, i.e., the number of theoretical stages $N_p$, as the measure of column efficiency.

### 1.4.2 Simulated moving bed

A schematic of the SMB unit considered in this work is shown in Figure 1: it is constituted of eight columns distributed according to a 2-2-2-2 configuration, i.e., two columns per section. Therefore, the model describing this SMB unit is constituted of one set of the equations reported in the previous section for each column, i.e., either the lumped solid diffusion equations (1.35) to (1.37) or the equilibrium axial dispersion equations (1.38), together with the single component and overall material balances at the four inlet and outlet nodes of the unit. At every instant of time equal to an integer multiple of the switching time, $t^*$, the ports of the inlet and outlet streams are moved one column forward in the direction of the fluid flow. Thus, the space composition profiles at the end of the previous period, i.e. at time $nt^*$, are used as initial conditions for the next integration from time $nt^*$ to $(n + 1)t^*$. Whatever the model used, after space discretisation, the partial differential equations are reduced to a system of ordinary differential equations, which is integrated in time using a commercial stiff integrator. Mass balances at the nodes and boundary conditions are written in terms of the concentration at the end points of the relevant columns and directly substituted in the system of ordinary differential equations of the SMB model.

It is worth noting that when using the solid diffusion model the axial dispersion coefficient is calculated in every section of the unit using the Chung and Wen equation52 and neglecting the molecular diffusion contribution; this yields the following relationship for the number of dispersion stages which is independent of the fluid flow rate and is the same for all solutes:

$$N_{disp} = \frac{L}{10c_d p}.$$  (1.44)

Due to Eq. (1.39), a different number of theoretical stages in the different sections of the SMB unit are used. On the other hand, if the axial dispersive model is used and the algorithm described above is implemented using the same number of grid points in each section of the unit, then a further approximation is introduced. This is not critical in the
context of the analysis carried out in this work, provided that the number of grid points is chosen as the smallest one among those exhibited by the different sections of the unit.
Chapter 2

Non-constant selectivity binary systems

At present Triangle Theory is available only for stoichiometric and non-stoichiometric Langmuir isotherms. In this case in fact the relevant steady state partial differential equations can be solved explicitly through an appropriate orthogonalization technique, i.e., the $\omega$-transformation or the equivalent $h$-transformation. However, this technique is not general and it has been developed only for the isotherms mentioned above, which are suitable to describe competitive adsorption equilibria only in the case of constant selectivity. In many cases of practical interest, this limitation is too strict since the complex adsorbate-adsorbate or adsorbate-adsorbent interactions lead to selectivities which vary with composition. Examples are several chiral separations, where the enantiomers to be separated interact with both chiral and achiral sites of the stationary phase and a bi-Langmuir isotherm may be used to describe the adsorption equilibrium data; in other cases more complex interactions require more complex models.

The aim of this chapter is to provide a procedure in the frame of Equilibrium Theory to calculate the boundaries of the complete separation region in the operating parameter plane $(m_2, m_3)$ and the critical values for $m_1$ and $m_4$ in the case of binary mixtures described by a general adsorption isotherm, including the case of selectivity changing with composition. The procedure is summarized while the details can be found elsewhere. The application of this approach to the bi-Langmuir isotherm, which is typically used to describe adsorption equilibria of enantiomers, and to the large class of systems whose equilibria can be described through the Ideal Adsorption Solution theory (IAS) are discussed.
2. Non-constant selectivity binary systems

2.1 Assumptions

In next sections the procedure to determine the complete separation region in the operating parameter space for a general adsorption isotherm is described; this approach is based on the theory of hyperbolic, reducible, homogeneous, first order partial differential equations.\(^6^5\)

It should be noted that the development of this approach requires that the adsorption isotherms satisfy the following conditions:

- the isotherms are purely competitive, i.e:
  \[
  \frac{\partial n_i}{\partial c_i} > 0 \quad i = A, B \quad (2.1)
  \]
  \[
  \frac{\partial n_i}{\partial c_j} < 0 \quad i \neq j \quad (2.2)
  \]

- the variation of \(c_i\) has a stronger influence on the adsorption of component \(i\) itself than on the adsorption of the other components, i.e:
  \[
  \frac{\partial n_i}{\partial c_i} > \left| \frac{\partial n_j}{\partial c_i} \right| \quad (2.3)
  \]

Note that conditions (2.1) and (2.3) imply that there exists a one-to-one mapping

Figure 2.1: Scheme of a two section counter current unit. Pure desorbent and regenerated solid enter section 2 and 3, respectively.
2.1 Assumptions

between fluid and adsorbed phase compositions, hence the equations:

\[ n_A = n_A(c_A, c_B) \]  
\[ n_B = n_B(c_A, c_B) \]

are invertible everywhere in the hodographic plane \((c_A, c_B)\). This can be readily seen by inspection of the Jacobian matrix of the mapping equations (2.4) and (2.5) in the case where Eqs (2.1) and (2.3) are satisfied. It is worth noticing that, as typical in most fine chemical applications, we are assuming that the components to be separated are diluted in an inert solvent, which plays the role of non adsorbable desorbent in the separation.

- the pure component isotherms are favorable for any given value of the other component:

\[ \left( \frac{\partial^2 n_i}{\partial c_j^2} \right)_{c_j} < 0 \]

By inspection of the above conditions it appears that these are typical of favourable, competitive isotherms which are by far the most common in applications: this is confirmed by the application to the bi-Langmuir and IAS model to be discussed later.

On top of that we assume that the transitions connecting two points in the hodograph plane are always shocks or simple waves, combined situations as combined waves (such as semi-shocks) being excluded. The stability conditions that guarantee these assumptions for transitions in the two section TCC unit are better clarified in Appendix B. It is worth noting that these assumptions are always fulfilled by the Langmuir and the modified Langmuir isotherm. However, this is not necessarily the case for all types of isotherms, and there may be instances where strong differences in terms of sequence of transitions may arise. The procedure presented in the following to draw the region of separation can be applied only if the transitions connecting two points in the hodographic plane are shocks or simple waves, i.e., no combined waves are present. In other words the transitions pertaining to section 2 of the separation unit (see Figure 1.3), corresponding to elution steps, must be simple waves, whereas those pertaining to section 3, corresponding to adsorption steps, must be shocks. These prerequisites for the application of the method are stated in mathematical terms in Appendix B, where an algorithm to check the fulfilment of these conditions is presented.
2.2 Two section TCC unit

Let us consider the two section TCC unit shown in Figure 2.1, where we assume that both the desorbent and the solid phase fed to the unit contain neither component A nor component B, i.e., they have been somehow fully regenerated. Accordingly, both these states are represented in the hodograph plane in Figure 2.2 by the origin and therefore, as shown in Appendix A, the intermediate state $\mathbf{M}$ for sections 2 and 3 lies on the axis $c_A$ and $c_B$, respectively, i.e., $\mathbf{M} = \mathbf{M}_2 = (c_A^2, 0)$ in section 2 and $\mathbf{M} = \mathbf{M}_3 = (0, c_B^3)$ in section 3. In other words, state $\mathbf{M}_2$ is pure A and $\mathbf{M}_3$ is pure B.

![Figure 2.2: Transition paths in the (cA, cB) plane for section 3 (β → M3 → D) and section 2 (D → M2 → γ) in two section TCC unit. In a four section TCC unit the point D is replaced with δ and ε which represents the solid state entering section 3 and the fluid state entering section 2, respectively.](image)

Let us now determine separately for each of the two sections of the unit the kind of steady-states which guarantee complete separation, based on the conditions for complete separation in terms of single species fluxes, i.e., Eqs (1.8) to (1.11) and on the Equilibrium Theory analysis of the single counter-current section summarized above. At this stage, the feed stream and streams $\beta$, entering section 3 as a fluid, and $\gamma$, representing the solid entering section 2, are considered not to be coupled; they all fulfill the requirement of containing both components A and B. The result can be summarized in the following theorem, whose proof is reported in:41
2.3 The complete separation region

**Theorem**: necessary and sufficient conditions for complete separation in the two section TCC unit in Figure 2.1 are that the two sections operate at the intermediate states $M_2 = (c_A^3, 0)$ and $M_3 = (0, c_B^3)$.

2.3 The complete separation region

Using the above theorem, the requirement of having simple waves in section 2 and shock waves in section 3, the conditions to achieve complete separation in a two section TCC unit can be cast as follows:

\[ \beta_1 |_{M_2} = m_{2, \text{min}} \leq m_2 \leq m_{2, \text{max}} = \beta_2 |_{M_2} \]

\[ \beta_1 |_{M_3 \rightarrow D} = m_{3, \text{min}} \leq m_3 \leq m_{3, \text{max}} = \beta_2 |_{\beta \rightarrow M_3} \]

The boundaries of the complete separation region are defined by the relationships obtained when $m_2$ and $m_3$ attain the upper and lower bounds in the previous inequalities. Using the results of Appendix A, these can be written as follows:

\[ m_{2, \text{min}} = \frac{\partial n_B}{\partial c_B} |_{M_2} \]

\[ m_{2, \text{max}} = \frac{\partial n_A}{\partial c_A} |_{M_2} \]

\[ m_{3, \text{min}} = \frac{n_B^3}{c_B^3} \]

\[ m_{3, \text{max}} = \frac{n_B^3 - n_B^3}{c_B^3 - c_B^3} = \frac{n_A^\beta}{c_A^\beta} \]

where the superscripts 3 and $\beta$ refer to the states $M_3$ and $\beta$, respectively.

Before analysing the above equations to gain more insight about the boundary of the complete separation region, it is worth noting that the states $\beta$ and $\gamma$ in Figures 1.3 and 2.2 are in general different, though coupled through mass balances at the bottom of section 3. However, when $m_3 = m_{3, \text{max}}$, then $\beta = \gamma$ as illustrated in Figure 2.3. In this case in fact the mass balances at the bottom of section 3 are:

\[ (m_3 + \frac{\varepsilon_p}{1 - \varepsilon_p}) c_A^\beta - n_A^\gamma - \frac{\varepsilon_p}{1 - \varepsilon_p} c_A^\gamma = 0 \]

\[ (m_3 + \frac{\varepsilon_p}{1 - \varepsilon_p}) c_B^\beta - n_B^\gamma - \frac{\varepsilon_p}{1 - \varepsilon_p} c_B^\gamma = m_3 c_B^\beta - n_B^3 \]

where the superscript $\gamma$ refers to the state $\gamma$. Combining these with Eqs (2.12) proves that indeed $c_i^\beta = c_i^\gamma$ and $n_i^\beta = n_i^\gamma$, for $i = A, B$. It is worth observing that in this case the net
fluxes of components A and B through section 3 given by Eq. (1.5) can be recast using Eq. (2.12) in terms of the state $\beta$:

$$f_i^3 = Q_s(1 - \varepsilon_p)(m_3c_i^\beta - n_i^\beta) \quad (i = A, B). \quad (2.15)$$

With reference to Figure 2.3, it can be seen that since points $\beta$ and $\gamma$ coincide, then the two paths corresponding to sections 2 and 3, i.e. $\beta \rightarrow M_3 \rightarrow D$ and $D \rightarrow M_2 \rightarrow \gamma$, constitute a closed loop. Moreover note that the feed state is different from $\beta = \gamma$ and that states $\alpha$, $\beta$ and $F$ are on a straight line due to the constraint provided by the material balance at the feed node.

![Figure 2.3: Transition paths in the ($c_A, c_B$) plane in a two section TCC unit for the optimal operating point w at a feed concentration of $c^F = 2.9$ g/l. The bi-Langmuir isotherm parameters are: $\gamma_A = 3.728$, $\delta_A = 0.3$, $a_A = 0.0466$ g/l, $b_A = 3$ g/l, $\gamma_B = 2.688$, $\delta_B = 0.1$, $a_B = 0.0336$ g/l, $b_B = 1$ g/l.](image)

Let us now analyze each portion of the boundary in detail; the same notation adopted in the previous chapter is used (see Figure 1.5, which is calculated for a system described by a Langmuir isotherm). In all the following four cases the overall mass balances for components A and B under the assumption of complete separation must be fulfilled:

$$\begin{align*}
(m_3 - m_2)c_A^F &= n_1^2 - m_2c_A^2 \quad (2.16) \\
(m_3 - m_2)c_B^F &= m_3c_B^3 - n_2^3 \quad (2.17)
\end{align*}$$

**Curve ab:** $m_3 = m_{3,\text{min}}$, Eq. (2.11).
In this case the r.h.s. of Eq. (2.17) is zero, hence \( m_3 = m_2 \). This yields the portion \( ab \) of the diagonal; the coordinates of points \( a \) and \( b \) are the Henry's constants of components A and B, respectively, i.e., the slope of the single component isotherm at zero concentration.

**Curve wb:** \( m_2 = m_{2, \text{min}}, \) Eq. (2.9).

Let us take \( c_A^2 \) as running parameter along this part of the boundary, starting from point \( b \) on the diagonal; here the fluid flow rate is zero and \( c_A^2 \) is also necessarily zero. With the chosen value of \( c_A^2 \), \( m_2 \) is obtained from Eq. (2.9). Substituting into Eq. (2.16) yields the corresponding \( m_3 \) value. The end point \( w \) of the curve is obtained as intercept with \( wr \) (see below).

**Curve ra:** \( m_2 = m_{2, \text{max}}, \) Eq. (2.10).

Eq. (2.10) is now applied to calculate \( m_2 \), using again \( c_A^2 \) as running parameter (initial value, \( c_A^2 = 0 \)) and Eq. (2.16) to obtain \( m_3 \). It is worth noting that this portion of the boundary depends only on the pure component isotherm of component A. The end point \( r \) is the intercept with curve \( wr \). It is worth noting that due to the use of Eq. (2.16), curves \( wb \) and \( ra \) depend only on \( c_A^F \) rather than on the whole composition of the feed.\[38\]

**Curve wr:** \( m_3 = m_{3, \text{max}}, \) Eq. (2.12).

As discussed above in this case \( \beta = \gamma \), hence Figure 2.3 applies and the determination of this part of the boundary is more difficult than in the previous cases. Beside the two Eqs (2.12) and the overall balances for A and B, i.e. Eqs (2.16) and (2.17), another constraint is that the states \( \beta \) and \( M_2 \) must belong to the same \( \Gamma_1 \), i.e., they must be obtained one from the other through integration along \( \Gamma_1 \) according to the procedure described in Appendix A. These five constraints allow to determine the five unknowns \( m_2, m_3, c_A^2, c_A^\beta \) and \( c_B^\beta \) once a value of the running parameter along \( wr \) \( c_B^3 \) is given. An upper bound for \( c_B^3 \) is provided by the value obtained from Eqs (2.12) when \( c_A^\beta = c_A^F \). It is worth noticing that in the optimal point \( w \) Eqs. (2.9) and (2.12) are fulfilled together with the overall mass balances for A and B under complete separation. This means that in \( w \) the \( m_2 \) and \( m_3 \) parameters are, respectively, the smallest and largest achievable to realise the constant states required by the theorem introduced at the end of the previous section. The solution of the four algebraic equations plus the ordinary differential equation, though in principle always feasible, may in practice be rather cumbersome for complex isotherms. This is particularly true since the conditions for the applicability of the method must be controlled during the determination of this
portion of the boundary of the complete separation region, as discussed in Appendix B.

2.4 Four section TCC unit

The four section TCC unit shown in Figure 1.3 can be regarded as the two section unit where two more sections have been added. Section 1 at the bottom is used to regenerate the solid, and section 4 at the top to regenerate the desorbent. In this way we can obtain a complete process including the regeneration steps. This poses two problems: the first is how to design the operating parameters $m_1$ and $m_4$ in sections 1 and 4, respectively, so as to make sure that the regeneration processes are properly performed; this is of the greatest importance since the expected separation regimes determined by the position of the operating point in the $(m_2, m_4)$ plane are attained only if a complete regeneration is achieved in sections 1 and 4.\textsuperscript{32,33,46} The second is whether and how the analysis developed for sections 2 and 3 with reference to the two section TCC unit can be extended.

First, let us analyze the regenerating sections. The same principles mentioned earlier can be applied to this case even in a more simple way, because only single component adsorption is involved, provided that complete separation is achieved in sections 2 and 3. Since both pure isotherms are assumed to be favorable as to Eq. (2.6), one can easily prove that the single transition occurring from the state of pure B to the pure solid state in section 4 is a $\Sigma$ shock, i.e., corresponding to adsorption of B on a regenerated solid phase, while on the other hand the transition between the pure fluid state and the state of pure A in section 1 is a $\Gamma$ simple wave, i.e., corresponding to elution of an adsorbed species.

In section 4 the prevailing steady state must be the solid state, i.e., B entering the column must be completely adsorbed and carried downwards to the raffinate node. The corresponding constraint on the flow rate ratio is:

$$\frac{\varepsilon_p}{\varepsilon_p - 1} \leq m_4 \leq m_{4,max} = \frac{n_B (c_B^R)}{c_B^R},$$

where $m_{4,max}$ is the value that lets the shock transition corresponding to the adsorption front of B standing in section 4,\textsuperscript{66} whereas $m_4$ attains the l.h.s. of the inequality when $Q_4 = 0$ and the separation unit is operated with three sections only.\textsuperscript{35} The raffinate concentration $c_B^R$ can be obtained from the overall mass balance of B in a four section TCC unit under the assumption of complete separation:

$$(m_3 - m_2)c_B^R = (m_3 - m_4)c_B^R.$$
Therefore, the value of $m_{4,cr}$ depends on the values of $m_2, m_3$ and $c_B^0$. Due to Eq. (2.6), Eq. (2.18) indicates that $m_{4,max}$ decreases when $c_B^0$ and $c_B^I$ increase and that its maximum value is the Henry constant of species B, i.e. the infinite dilution slope of its isotherm, $H_B$.

In section 1 the prevailing steady state must be the fluid state, so that component A is completely desorbed by the fluid flow and carried upwards to the extract node. This condition is guaranteed by the condition:

$$m_1 \geq m_{1,min} = \left. \frac{dn_A(c_A)}{dc_A} \right|_{c_A=0} = H_A. \quad (2.20)$$

When the two constraints (2.18) and (2.20) are fulfilled, it is guaranteed that the fluid stream entering section 2 contains some component A, but no B, while on the other hand the solid stream fed to section 3 has some component B adsorbed, but no A. Therefore with reference to Figure 2.2, these states correspond in the hodograph plane to points ε and δ, respectively. The second issue about four section TCC units is exactly whether this new situation may affect the values of $m_2$ and $m_3$ leading to complete separation, that have been computed above for the two section TCC unit. The answer is negative due to three facts. First, also in the four section unit sections 2 and 3 must attain the intermediate states $M_2$ and $M_3$ to achieve complete separation, as proved in Appendix C. Secondly, among the four constraints defining the boundaries of the complete separation region, i.e. Eqs (2.9) to (2.12), three depend on states $\beta$, $M_2$ and $M_3$, whereas only $m_{3,min}$ is given by a different relationship involving the state $\delta$. Since $m_3 = m_{3,min}$ leads to $f_B^3 = 0$, also in a four section TCC unit this condition is mapped onto the diagonal of the $(m_2, m_3)$ plane. Finally, under complete separation conditions for both the two and the four section units with the same feed composition and the same choice of $m_2$ and $m_3$ the overall material balances (2.16) and (2.17) must be fulfilled; these obviously yield the same $M_2$ and $M_3$ states, which combined with the same feed state yield the same state $\beta$, hence the same conditions for complete separation (2.9), (2.10) and (2.12) as required by the statement.

Thus, it can be concluded that the complete separation region obtained in the previous section for the two section TCC unit, applies also to the four section TCC unit provided that $m_1$ and $m_4$ fulfil the relevant constraints (2.18) and (2.20).

### 2.5 Results and discussion

Let us now investigate a few applications of the developed procedure which are not possible using the standard Triangle theory. First, the complete separation region is determined for
systems characterized by the binary bi-Langmuir isotherm. Secondly, the general validity of the developed procedure is shown with reference to systems described by the general multicomponent equilibrium model based on the Ideal Adsorbed Solution theory; in particular the case where single component Langmuir isotherms are combined according to IAS theory to describe the competitive adsorption of a binary mixture is presented and discussed. Finally, a short-cut method to determine an approximate region of complete separation is introduced and compared with the results of the rigorous approach presented above.

2.5.1 Bi-Langmuir isotherm

Let us consider the binary bi-Langmuir isotherm, i.e.:

\[
n_i = \frac{\gamma_i c_i}{1 + \sum_{j=A,B} a_{ij} c_j} + \frac{\delta_i c_i}{1 + \sum_{j=A,B} b_{ij} c_j} \quad (i = A, B)
\]  

(2.21)

This favorable isotherm is well-known in chromatography and is often used to describe adsorption on two independent sites, which is the case of a number of enantioseparations. The adsorbed amount in the stationary phase is given by the sum of two Langmuir terms. Usually one term accounts for the adsorption on non-chiral selective sites with high saturation capacity, while the other accounts for adsorption on chiral sites with low saturation capacity.\(^{62,67}\) In many cases of applicative interest, the non-constant selectivity behavior exhibited by enantiomers on chiral stationary phases is properly described by this model.

The bi-Langmuir isotherm can also be used as an empirical model to describe systems with selectivity strongly changing with composition, since it provides four parameters for each component to fit the equilibrium data.

Note that the Langmuir model can be obtained as a special case of the bi-Langmuir isotherm by letting \(b_i = \delta_i = 0\) in Eq. (2.21), and the modified Langmuir model by letting \(\delta_i = h\) and \(b_i = 0\). The linear case, which is obtained by letting \(a_i = b_i = 0\), is of particular interest because it represents the limit behaviour of Eq. (2.21) in the case of very dilute solutions.

It is seen that in all these cases the results already published in the literature are coherent with the approach presented in this paper.

Let us consider the separation of the enantiomers of 1-1'-bi-2-naphtol on a 3,5-dinitrobenzoyl phenylglycine bonded to silica gel stationary phase, using a mixture of heptane-hexane (78:22) as mobile phase.\(^{13}\) The bi-Langmuir isotherm parameters are reported in the caption of Figure 2.3.

The region of complete separation at a feed concentration for both enantiomers is \(c_A^f = c_B^f = 2.9\) g/l is drawn in Figure 2.4. The region has a triangular shape where, contrary to
Figure 2.4: Plot of the regions of separation in the \((m_2, m_3)\) plane for the bi-Langmuir (solid line) and Langmuir (broken line) models. Parameters for bi-Langmuir as in Figure 2.3. Langmuir parameters: \(H_A=4.028\), \(k_A=0.0503\) g/l, \(H_B=2.788\), \(k_B=0.0348\) g/l.

the Langmuir case, the boundary wb, whose equation can still be written in a closed form since \(c_A^2\) can be explicitly obtained from Eq. (2.9), is a curve and not a straight line. The complete separation region is surrounded by three more regions, corresponding to different separation regimes: pure extract, pure raffinate and no pure outlet, i.e. both components distributed in the outlet stream. Based on the graphical representation reported in Figures 1.5 and 2.4, from the relative position of the operating point with respect to the four regions, the SMB separation performance can be predicted, provided that the constraints discussed in section 3.4 on the regenerating sections are fulfilled. It is worth recalling that point w represents the optimal operating point in terms of process performance.

For a comparison, in Figure 2.4 the separation region computed with a Langmuir isotherm is shown with broken boundaries. Its parameters are determined such that the Langmuir isotherm describes as accurately as possible the equilibrium data obtained through the bi-Langmuir isotherm that was used to calculate the separation region with solid boundaries. Although the single component Langmuir and bi-Langmuir isotherms are very close, being the difference in the adsorbed phase concentration predicted less than 6%, the separation regions are different. In particular the operating points w and w' are far away. The difference is due to the decrease in selectivity predicted by the bi-Langmuir model. This effect will be analysed more in details in the next section.
Figure 2.5: Effect of the total feed concentration on the region of complete separation in the 
\((m_2, m_3)\) plane for a system described by a bi-Langmuir adsorption isotherm. Isotherm parameters 
as in Figure 2.3. \(c^F_A = c^F_B = c^F_F / 2\). \(1\) \(c^F_F = 5.8 \text{ g/l}\), \(2\) \(c^F_F = 3 \text{ g/l}\), \(3\) \(c^F_F = 1.4 \text{ g/l}\); \((-\ -\ -\) region 
of separation in the linear case, i.e. when \(c^F_T \rightarrow 0\).

The developed model is rather useful to gain insight about the effect of feed composition on 
the SMB behavior, which is one of the main operating variable in industrial applications; 
this is done in Figures 2.5. The same separation with the same feed ratio of the components 
to be separated but different values of the overall feed concentration is considered. Figure 
2.5 illustrates that when the overall feed concentration increases from infinite dilution 
(corresponding to the dashed right triangle) to larger values the complete separation region 
becomes smaller and sharper. The optimal point shifts towards the lower left corner of the 
\((m_2, m_3)\) plane and the best feed concentration has to be chosen as a compromise between 
process performance, which improves for larger values of \(c^F_T\), and robustness, that becomes 
instead smaller, similarly to the case of Langmuir isotherms.

2.5.2 IAS model

A rather powerful tool for the description of complex adsorption equilibria where selectivity 
is a strong function of composition and adsorbate-adsorbate interaction are observed is 
provided by the Real Adsorbed Solution Theory. Although the developed approach could 
be applied in principle to this model, for the sake of simplicity we investigate its application
to the case where the pure component isotherms are Langmuir isotherms and the adsorbed phase behaviour is ideal. The following set of ten equations in the ten unknowns $n_t$, $z_t$, $c_i^0$, $n_i^0$, $n$ and $\Psi$ ($i = A, B$), which can be solved in terms of $c_A$ and $c_B$, describe the adsorption equilibrium:

\[ c_i = z_i c_i^0 \quad (i = A, B) \quad (2.22) \]
\[ \Psi = \int_0^{c_i^0} \frac{n_i^0(x)}{x} \, dx = N_i \ln(1 + K_i c_i^0) \quad (i = A, B) \quad (2.23) \]
\[ 1 = z_A + z_B \quad (2.24) \]
\[ n_i^0 = \frac{N_i K_i c_i^0}{1 + K_i c_i^0} \quad (i = A, B) \quad (2.25) \]
\[ n_t = \left( \frac{z_A}{n_A^0} + \frac{z_B}{n_B^0} \right)^{-1} \quad (2.26) \]
\[ n_i = n_t z_i \quad (i = A, B) \quad (2.27) \]

Here $\Psi$ represents the excess surface potential, which is proportional to the spreading pressure in the case of surface adsorption. An interesting situation arises in the case where the pure components exhibit different saturation concentrations, i.e. $N_A \neq N_B$ in the corresponding Langmuir isotherm. In this case the IAS model fulfils the Gibbs adsorption isotherm (2.23) and accounts for the effect of composition on selectivity. On the contrary the empirical constant selectivity multicomponent Langmuir model based on the same pure component isotherms,

\[ n_t = \frac{N_i K_i c_i}{1 + K_A c_A + K_B c_B} \quad (i = A, B) \quad (2.28) \]

is thermodynamically inconsistent. The two models coincide only when $N_A = N_B$. It should be emphasized that the IAS model is considered to be the correct one for ideal solutions, the binary Langmuir model being just its empirical approximation.

Let us now compare the complete separation region obtained with the multicomponent Langmuir isotherm, given by known explicit relationships in terms of the feed composition, and those obtained using the IAS for which the developed procedure has to be applied. It is also worth noting that while in the first case selectivity is constant in the second one it changes with composition. Two cases are considered as reported in Table 2.1, in all of which the Henry constants of A and B, i.e. $H_i = N_i K_i$, have been kept constant, but the ratio $N_A/N_B$ has been changed, taking the values 4 and 0.25.

The case where this ratio is one is trivial, because in this case the two models coincide. The behaviour of selectivity, defined as:

\[ S = \frac{n_A}{c_A/c_B} \quad (2.29) \]
Table 2.1: values of the single component Langmuir isotherms used for the calculations reported in Figures 2.7 and 2.8. The total feed concentrations $c_F^e$ and the saturation capacities $N$ are in g/l, the $K$ values in l/g. The feed composition is equimolar.

<table>
<thead>
<tr>
<th>System</th>
<th>$N_A$</th>
<th>$N_B$</th>
<th>$K_A$</th>
<th>$K_B$</th>
<th>$c_F^e$</th>
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</thead>
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<tr>
<td>a</td>
<td>4</td>
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<td>1</td>
<td>2</td>
<td>0.30</td>
</tr>
<tr>
<td>b</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>0.5</td>
<td>0.20</td>
</tr>
</tbody>
</table>

as a function of the concentration of A or B for an equimolar mixture is illustrated in Figure 2.6.

Figure 2.6: Comparison between IAS model (solid lines) and multicomponent Langmuir isotherm (broken line). Selectivity as a function of the total fluid concentration $c_T$ for an equimolar mixture. The parameters for cases (a-b) are reported in Table 2.1.

It can be seen that according to the multicomponent Langmuir model $S = 2$ in all cases at all fluid concentrations, while in the case of the IAS model selectivity increases or decreases for increasing values of $c_A$ and $c_B$, depending on whether the ratio $\Gamma_A/\Gamma_B$ is larger or smaller than one, respectively.

In Figures 2.7 and 2.8 the complete separation regions calculated with the binary Langmuir isotherm and with the IAS model are compared. It appears that in all four cases the IAS prediction is rather different from the complete separation region obtained with the binary Langmuir isotherm.
2.5 Results and discussion

Figure 2.7: Comparison between IAS model (solid lines) and multicomponent Langmuir isotherm (broken lines). Regions of complete separation in the \((m_2,m_3)\) plane for the different system \((a)\) of Table 2.1.

In particular the error made using the Langmuir isotherm in predicting the optimal operating point under the assumptions of Equilibrium theory, i.e., the vertex of the triangle, is rather large for systems \((a)\) and \((b)\). Moreover, the IAS “triangle” is smaller when \(N_A < N_B\) and larger when \(N_A > N_B\) than the region calculated with the binary Langmuir isotherm. The left hand side boundary of the complete separation region, i.e. line \(wb\), is curved and it is convex in the former case and concave in the latter. Finally, the tail of the complete separation region for high values of \(m_2\), i.e. the portion \(ra\) of the boundary coincides using the two models. This is consistent with the fact that Eq. (2.10), which is used to calculate \(ra\), depends only on the pure component \(A\) isotherm, which is the same for the two models.

This regular pattern of behavior can be explained by analysing how selectivity changes with composition as illustrated in Figure 2.6. Let us refer to system \((a)\); in this case the selectivity exhibited by the IAS model increases with respect to the constant Langmuir value when the concentration of the fluid increases. The average concentration in the TCC unit, as well as in the equivalent SMB, is larger for larger values of the difference \((m_3 - m_2)\), i.e., for operating points far from the diagonal. It follows that when the IAS model is used the TCC unit experiences selectivity values larger than when the binary Langmuir model is adopted; hence the complete separation region predicted using the former model is larger than the one calculated with the latter, thus indicating an easier and potentially more efficient separation.
2.5.3 Short-cut method

In this section we develop a short-cut method which allows, with a much simpler mathematical procedure, to estimate a good approximation of the complete separation region given by the general procedure developed above. This appears particularly reasonable when considering that the Equilibrium theory approach is anyhow approximate and therefore adding further approximation may be to a certain extent acceptable. The Equilibrium the-
ory model is in fact based on a simplified description of the adsorption column dynamics where mass transfer resistance and axial mixing are neglected. The effect of these dispersive phenomena on SMB performance can be accounted for using detailed models, as discussed by.\textsuperscript{32} In practice, dispersive phenomena shrinks the complete separation region obtained through Equilibrium theory. On the other hand, the adsorption equilibrium model adopted to describe the system of interest inevitably contains some approximations due to our limited understading of adsorption on complex stationary phases, such as the ones used in chiral separations. In all cases, as we will see later, the errors introduced by the short-cut method are of the same order of magnitude as inherent inaccuracies of the Equilibrium Theory described above. The most valuable information given by Triangle theory refers to the position of the optimal operating point in the operating parameter space as a function of feed composition, as illustrated in Figures 2.4 and 2.5 in the case of the bi-Langmuir isotherm. This information allows the practitioner to choose a reasonable feed composition as a compromise between productivity and process robustness, to give a prediction of the process performance and to initialize effectively a process optimizer which uses a detailed model of the TCC or SMB unit. It is worth pointing out that the effect of changing the feed composition on the shape and position of the complete separation region is indeed the key advantage provided by Triangle theory. In fact, although a rough location of the optimal operating point is obtained through the knowledge of the Henry's constants of the components to be separated, i.e., assuming linear conditions for the separation, this is clearly a rather unsatisfactory approximation in most cases.\textsuperscript{37,46}

This information can be achieved through the following simplified procedure, where it is assumed that a competitive binary isotherm for the system under examination is available. In other words, the relationships (2.4) and (2.5) are known and the conditions of Eqs (2.1) to (2.6) are fulfilled. A further assumption is made, i.e. that the conditions discussed in Appendix B are fulfilled, even though there is no way to check them when applying the short-cut method.

With reference for example to Figure 2.9, curves \textbf{wb} and \textbf{ra} of the boundary of the complete separation region are calculated using the procedure described in section 2.2. In fact Eqs (2.9) and (2.10) are simple enough to be handled in the most general case, and in the important case of bi-Langmuir isotherm and IAS model explicit relationships for lines \textbf{wb} and \textbf{ra} can be easily obtained.

The most difficult step of the general procedure is the calculation of curve \textbf{wr}, which reflects the strong coupling between the two central sections of the TCC unit. The short-cut method consists in substituting the correct curve \textbf{arw} with the approximate line \textbf{aw}' which is given
by the following two relationships, obtained by combining Eqs (2.12), Eq. (2.15) and (2.17):

\[
m_3 = \frac{\eta_\beta^A}{c_A^\beta} \quad (2.30)
\]

\[
m_2 = m_3 + \frac{\eta_\beta^B - m_3 c_B^\beta}{c_B^F} \quad (2.31)
\]

If these equations were applied using the composition of state \( \beta \) properly coupled to the feed state and to states \( \alpha \) and \( \gamma \) (see Figure 2.3), then the correct curve \( rw \) would be obtained. However, one may observe that point \( \beta \) in the hodograph plane is confined in the region between the origin and the feed state. Thus, as a first approximation it can be assumed that the state \( \beta \) is located on the straight line \( D \rightarrow F \). This implies choosing values of \( c_A^\beta \) between zero and \( c_A^\infty \), and accordingly \( c_B^\beta = c_A^\beta c_B^F / c_A^\infty \). Entering this set of values into Eqs (2.30) and (2.31) leads directly to the coordinates of the points on the line \( ar'w'a' \) in Figure 2.9. It is worth noting that when \( c_A^\beta = 0 \), the above equations yield the coordinates of point \( a \), i.e., \( (H_A, H_A) \). This is why this curve is taken as an approximation also of line \( ra \), which is replaced by it.

![Figure 2.9: Regions of complete separation calculated with the rigorous procedure (solid lines) and with the short-cut method (broken lines) for a bi-Langmuir isotherm (see Figure 6 for the parameters). \( c_A^F = c_B^F = c_T^F / 2 \). a) \( c_T^F = 5.9 \) g/l. The optimal operating point \( w' \) calculated with the short-cut approach is close to the point \( w \).](image)

Based on these observations the short-cut algorithm reported in Table 2.5.3 and illustrated in Figure 2.9(a) is proposed.
2.5 Results and discussion

<table>
<thead>
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<th>Curve bwb'</th>
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<table>
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<tr>
<th>Point w'</th>
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<tr>
<td><strong>step 8</strong></td>
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</table>

Table 2.2: *short-cut procedure for the calculation of the approximate complete separation region in the $(m_2,m_3)$ plane.*
The short-cut method is remarkably accurate in predicting the position of the optimal operating point and it is also able to reproduce qualitatively the effect of changing feed concentration on the shape of the complete separation region.\textsuperscript{41} It is worth noting that the accuracy of the short-cut method is not very good at rather small values of \((m_3 - m_2)\) which are anyway not very attractive in practice since they correspond to low productivity. It should be remarked that lines \(w'b'\) and \(w'a'\) have no physical meaning since they have been obtained by enforcing the overall material balances (2.16) and (2.17), which hold true only under complete separation conditions.

This analysis proves that the short-cut method may be a rather effective tool to determine approximate complete separation regions for two kinds of systems: those described by complex isotherms for which the exact procedure reported in section 3.3 is not doable and those described by isotherms such as bi-Langmuir or IAS for which the exact procedure is feasible, but does not lead to close algebraic expressions as in the Langmuir case. Whenever an algebraic first approximation of the exact region of complete separation is required the short-cut algorithm in Table 2 provides very fast and rather accurate information. The key drawback of this method is that it does not allow to check the prerequisites for the application of the theory presented in this work.\textsuperscript{41} For this one has to rely on physical intuition.
Chapter 3

SMB with extracolumn dead volume

The technical realisation of the large scale Sorbex process involves a single vessel, divided in a number of subsections, usually 12. This solution is not convenient at a small scale, where SMBs are constituted of a set of columns properly connected by a system of valves and tubing. In this kind of SMB units the extracolumn dead volumes, though kept carefully at a minimum extent, become comparable to the column volume and cannot be neglected, in particular when designing the operating conditions. The importance of accounting for this effect has already been recognised in the literature, but no detailed analysis, either experimental or theoretical, has been reported. The common opinion is that extracolumn dead volumes hinder high separation performance, by introducing harmful extracolumn band broadening.

The objective of this chapter is to fill this gap by studying the effect of dead volumes on the performance of SMB units. These theoretical findings are assessed by discussing experimental results relative to the separation of the Tröger’s base enantiomers on microcrystalline triacetylcellulose, in a 8 column SMB unit where the extracolumn dead volume is 40% of the column volume.

3.1 SMB model

The SMB unit can be modeled as a closed loop of chromatographic modules, as illustrated in Figure 1.1 where a 2-2-2-2 configuration has been considered. Each chromatographic module (see Figure 3.1) consists of three parts: two empty dead volumes and the chromatographic column. The dead volumes are assumed to be located at the beginning and at the end of the column. Since the theoretical analysis in section 3 shows that the actual distribution
of the dead volumes has no influence on the results, the layout in Figure 2 is as general as anyone else having an overall dead volume of \( V_D \). After space discretisation, the model of a chromatographic module is made of a system of ordinary differential equations accounting for both the dead volume and the chromatographic column. The chromatographic module models are coupled through the mass balances at the nodes between adjacent modules, which involve also the inlet and outlet streams to the unit (see Figure 1.1). When the integration time is equal to an integer multiple of the switch time \( t^* \), the position of the inlet and outlet ports is shifted forward in the direction of the fluid flow. Then a new integration in time is started, using the composition profile reached before the switch occurring at \( t^* \) as new initial condition.

![Figure 3.1: scheme of the chromatographic module of an SMB unit, with (a) and without (b) dead volumes. The solid arrow indicates the position of an inlet stream in the time \( 0 \leq t \leq t^* \); the broken arrow indicates its position after the switch occurring at \( t = t^* \).](image)

### 3.2 Linear Equilibria

First, let us consider a SMB unit where the components to be separated are simply characterized by linear adsorption equilibria (1.16). The separation of interest is between species A and B, where \( H_B < H_A \), i.e., A and B are the more and less retained component, respectively. The residence time in the module illustrated in Figure 3.1 is made of two contributions, the first given by the residence time in the extracolumn dead volume and the second by the
3.3 Nonlinear Equilibria

retention time in the chromatographic column:

\[ t_{i,j}^* = t_j^D + t_j^R = \frac{V_D}{Q_j} + \frac{V\varepsilon^*}{Q_j} \left[ 1 + \frac{1 - \varepsilon^*}{\varepsilon^*} H_i \right], \quad (i = A, B; \, j = 1, \ldots, 4). \quad (3.1) \]

It is rather obvious that under the previous assumptions \( t_{B,j}^* < t_{A,j}^* \).

Complete separation of \( A \) and \( B \) and regeneration of sections 1 and 4 of the SMB unit require that the following constraints are fulfilled:

- **Section 1**: \( t_{A,1}^* \leq t^*, \quad (3.2) \)
- **Section 2**: \( t_{B,2}^* \leq t^* \leq t_{A,2}^*, \quad (3.3) \)
- **Section 3**: \( t_{B,3}^* \leq t^* \leq t_{A,3}^*, \quad (3.4) \)
- **Section 4**: \( t^* \leq t_{B,4}^*, \quad (3.5) \)

Using Eq. (3.1) these inequalities can be recast in the following form:

- **Section 1**: \( H_A \leq \bar{m}_1, \quad (3.6) \)
- **Section 2**: \( H_B \leq \bar{m}_2 \leq H_A, \quad (3.7) \)
- **Section 3**: \( H_B \leq \bar{m}_3 \leq H_A, \quad (3.8) \)
- **Section 4**: \( \bar{m}_4 \leq H_B, \quad (3.9) \)

where the modified flow rate ratio \( \bar{m}_j \) is defined as follows:

\[ \bar{m}_j = \frac{Q_j t_j^* - V\varepsilon^*}{V(1 - \varepsilon^*)} - \frac{V_D}{V(1 - \varepsilon^*)} = m_j - m_D, \quad (3.10) \]

and in the right hand side of the last equation \( m_j \) is defined by Eq. (1.7) and \( m_D = V_D/(V(1 - \varepsilon^*)) \).

Eqs (3.6) to (3.9) are formally the same as those already reported in the literature for linear systems,\(^1,6,33\) but are now able to properly account for the effect of extracolumn dead volume through the new term \( m_D \). It is evident that whenever \( V_D \) is so small to be negligible the above equations reduce to the classical ones involving the parameters \( m_j \) only. Based on physical arguments, Eq. (3.10) has been used previously.\(^73\)

### 3.3 Nonlinear Equilibria

The SMB technique has been developed with the aim of finding a technologically feasible realization of an adsorptive countercurrent separator.\(^1\) Thus, in a SMB unit the countercurrent movement between the solid and the fluid phase is simulated in a discrete way, by
shifting periodically the inlet and outlet ports of the unit. The equivalence between a True Counter Current unit (TCC) such as the one illustrated in Figure 1.3 and a SMB configuration has not only a conceptual but also a practical importance, since it can be exploited for modeling and design purposes. As a matter of fact, the design problem for TCC units can be solved in the frame of Equilibrium Theory for a rather large class of systems described by many nonlinear adsorption isotherms of applicative interests, such as the Langmuir,\textsuperscript{33,36} modified Langmuir\textsuperscript{37} and bi-Langmuir adsorption isotherm,\textsuperscript{38,41} both in the binary\textsuperscript{37} and in the multicomponent case.\textsuperscript{34,39,40,74} These results are given in terms of the flow rate ratios in the TCC unit, $m_{j}^{TCC}$ ($j = 1, \ldots, 4$), which are defined as:

$$m_{j}^{TCC} = \frac{Q_{j}^{TCC} - Q_{s} \varepsilon_{p}}{Q_{s} (1 - \varepsilon_{p})},$$

where $Q_{j}^{TCC}$ and $Q_{s}$ are the fluid and the solid flow rate, respectively. As an example of application of this approach, the complete separation region in the $(m_{2}, m_{3})$ plane for the separation of a binary mixture characterized by a Langmuir isotherm using a nonadsorbable desorbent is illustrated in Figure 1.5.

The results obtained through Equilibrium Theory for TCC units can be applied to SMB units by exploiting their equivalence. In fact the two unit configurations achieve the same separation performances provided geometric and kinematic conversion rules given by the following relationships are fulfilled:\textsuperscript{1,75}

$$\frac{V}{t^{*}} = \frac{Q_{s}}{1 - \varepsilon_{b}}$$

$$Q_{j} = \left[ Q_{j}^{TCC} + \frac{Q_{s} \varepsilon_{b}}{1 - \varepsilon_{b}} \right],$$

where $Q_{j}$, with no superscript, refers to the SMB unit as in all previous equations. Using Eqs (3.12) and (3.13) it can be readily shown that the definition of $m_{j}^{TCC}$ (3.11) reduces to that of $m_{j}$ for SMB units given by Eq. (1.7). It follows that a result such as the one illustrated in Figure 6, which has been obtained by considering a TCC configuration and using the corresponding definition of $m_{j}^{TCC}$, i.e. Eq. (3.11), can be directly applied to SMB units by interpreting the coordinates of the diagram according to the definition of $m_{j}$, i.e. Eq. (1.7). The above results summarize the state of the art, where no account of extracolumn dead volume is made. Before looking for a possible extension, it is worth reconsidering the conversion rules (3.12) and (3.13) in order to deeply understand how they are obtained. Let us consider the fixed bed column of Figure 3.1(b), which is part of the $j$-th section of a SMB unit and has no extracolumn dead volume. At time zero an inlet port is located before the column, whereas after a time period $t^{*}$ this is shifted to the node immediately after the column. The fluid flow rate with respect to this inlet port taken as
reference position is made of two terms; a positive contribution due to the continuous fluid flow, with flow rate \( Q_j \), and a negative contribution due to the discrete jump of the whole column to the left of the inlet port occurring at time \( t^* \). Since the port switch is periodic, in the long run the latter contribution can be averaged, thus yielding a negative average fluid flow rate equal to \( V \varepsilon / t^* \). As far as the solid motion is considered, the fixed bed exhibits no movement in the positive direction but a periodic movement in the negative direction, which gives an averaged contribution equal to \( V (1 - \varepsilon) / t^* \). It can be readily seen that the fluid and solid flow rates in the equivalent TCC unit given by Eqs (3.12) and (3.13) correspond exactly to the averaged net effect of the continuous and discrete motion observed in a SMB unit and just described.

Now, let us consider a SMB unit and its nonnegligible extracolumn dead volume. First, it is worth observing that it does not make sense trying to find an equivalent TCC configuration with dead volume. This would imply the adoption of some unrealistic solid by-pass between columns and would also be ineffective, since a new Equilibrium Theory of TCC units with extracolumn dead volume should be developed. Therefore the idea is to look for a TCC configuration (with no dead volume, so that the whole body of knowledge developed so far about optimal design can be applied in a straightforward way) which is equivalent to a SMB configuration with extracolumn dead volume. In other words, we look for a new set of conversion rules which substitute the classical ones (3.12) and (3.13) used until now for systems where \( V_D = 0 \).

To this aim let us refer to Figure 3.1 (a), where the same column of Figure 3.1 (b) is preceded and followed by a \( V_D/2 \) dead volume. First let us calculate the net average fluid flow rate, accounting for both the continuous flow and the discrete jumps due to port switching, which in this case involves also the pre- and post-column dead volumes. The fluid flow rate in the equivalent TCC unit is given by this net average flow rate:

\[
Q_{j_{TCC}} = Q_j - \frac{V \varepsilon_b + V_D}{t^*}.
\]

The average solid flow rate is the same as in the case with no extracolumn dead volume, since the latter does not affect the discrete motion of the solid phase itself, thus Eq. (3.12) applies. Substituting Eqs (3.12) and (3.14) in the definition of \( m_{j_{TCC}} \) and accounting for Eq. (3.10), i.e., \( \overline{m}_j = m_j - m_D \), yields the equivalence \( m_{j_{TCC}} = \overline{m}_j \). This proves that in the general nonlinear case by applying the design criteria developed for TCC units (of which Eqs (3.6) to (3.9) for linear systems, and Figure 1.5 for nonstoichiometric Langmuir systems are special cases) to the modified flow rate ratio \( \overline{m}_j \) leads to the correct criteria for SMB units with extracolumn dead volume. As already noted, the case of no extracolumn dead volume is obtained as special case of the general relationships by letting \( V_D = 0 \).
3. SMB with extracolumn dead volume

3.4 Analysis of experimental results

In the previous section the role of extracolumn dead volume in the absence of important band broadening effects has been analysed. It has been shown that the definition of the generalized $\overline{m}$ parameter can account for the increased residence time in the chromatographic module. The effect of reduced separation efficiency due to extracolumn band broadening has been studied with a model. Numerical simulations where dispersion in dead volumes is considered allow to assess the role of backmixing in the dead volumes. These simulations demonstrate that the hindering effect of extracolumn dead volume on SMB separation performance depends on the size and the layout of the dead volume and on the extent of backmixing in it; the role of these two parameters has to be considered with respect to the size of the chromatographic columns and to the retention time in them, which depends on the adsorptivity of the species to be separated. The results of this analysis is that the effect of extracolumn band broadening and finite mass transfer rate and dispersion discussed in the next chapter is qualitatively similar. In fact, both dispersive phenomena shrink the separation region in the $\overline{m}$ space.

![Figure 3.2](image)

Figure 3.2: separation of the Tröger's base enantiomers on CTA. Operating points of the experimental runs and linear region of separation in the $(\overline{m}_2, \overline{m}_3)$ plane. The Henry constants for the Tröger's base enantiomers at 323 K are: $H_A = 4.38$ and $H_B = 2.18$. Symbols: (□) less than 98% purity in one of the outlet streams, (■) purities larger than 98%.

In this section, the experimental results obtained in a series of SMB experiments are
analysed in the light of the first effect, the increased residence time in the chromatographic module. These refer to the separation of the Tröger's base enantiomers on microcrystalline triacetyl cellulose using ethanol as mobile phase. The SMB unit has a 2-2-2-2 configuration, with 25 cm long columns (I.D. 46 mm) and $e^e = 0.56$. The extracolumn dead volume is about 40% of the column volume, i.e. $V_D = 1.75 \text{ cm}^3$ yielding $m_D = 0.9$, due to the presence of a check valve between each pair of columns.

![Figure 3.3: separation of the Tröger's base enantiomers on CTA. Operating points of the experimental runs and linear region of separation in the $(m_2,m_3)$ plane. Symbols as in Figure 3.2.](image)

Sixteen experiments were performed at a racemic feed concentration of 3 g/l; the corresponding operating points in the $(\bar{m}_2, \bar{m}_3)$ plane are shown in Figure 3.2. The linear complete separation region, taken in this case as a good approximation of the nonlinear triangle, is also shown; the nonlinear triangle cannot be calculated exactly due to the non Langmuirian behavior of the strongly adsorbed enantiomer. The closed circles (■) identify operating conditions achieving complete separation, which is defined as the performance where purity is larger than 98% in both extract and raffinate. Open squares (□) correspond to operating conditions where this requirement is not fulfilled. In particular, points above the linear triangle exhibit poor raffinate purity, whereas poor extract purity is achieved for points on the left hand side of the triangle. These results are in rather good agreement with model predictions and prove the correctness of the proposed approach to account for extracolumn dead volumes. As a further confirmation of that, it is worth noting that if the presence of extracolumn dead volumes were ignored and Eqs (3.6) to (3.10) with $m_D = 0$ were used,
then Figure 3.3 would be obtained, where the operating plane is spanned by \( m_2 \) and \( m_3 \) and the operating points are shifted upwards along the diagonal with respect to Figure 3.2. As a consequence points achieving high product purity in both outlet streams would lie outside the complete separation region, while on the other hand points failing to achieve 100% extract purity would lie inside the complete separation region, thus making theoretical predictions and experimental results not consistent at all.
The aim of this chapter is to address the issue of the nonideal effects, i.e. finite mass transfer and axial dispersion, on the SMB performance by determining the region of complete separation in the real case and by comparing it with the solution provided by the ideal Equilibrium Theory model. The study case considered is the separation of enantiomers in a non-adsorbable solvent, where the system is described by a bi-Langmuir isotherm. This is a rather general case, representative also of the Langmuir and modified Langmuir isotherms,\(^{37}\) which can be regarded as a special case of the bi-Langmuir isotherm.\(^{38}\) The region of complete separation has been determined by performing simulations using a detailed model on a fine square grid laid on the \((m_2, m_3)\) plane, while keeping the operating parameters for the first and last section of the SMB unit far away from their critical values. Since this procedure is computationally intensive and time-consuming, an equilibrium-dispersive model of the SMB, which accounts for dispersive effects, has been used.\(^{72,76}\) This is a rather realistic model, since axial dispersion and mass transfer resistances play a qualitatively similar role in determining the performances of chromatographic columns.\(^{77}\)

It is worth noting that the analytical results of the Equilibrium Theory, which are based on the TCC/SMB equivalence,\(^{29}\) have been compared directly with the cyclic steady state results of the SMB model. This is the only approach which can assess the deviation of Equilibrium Theory predictions from the performances of the real SMB model. A comparison with the TCC model with axial dispersion does not provide reliable answers in this regard. In fact, it is difficult to give a clear physical interpretation of the parameters in the TCC model; for instance, the HETP values for a fixed bed and a countercurrent one are different even though the relative velocity between the fluid and the solid phase is the same, i.e. even when the two units are kinetically equivalent.\(^1\) Moreover experimental concentration profiles along the SMB columns should be compared with results obtained using an SMB model\(^{72}\)
and not with simulated TCC profiles, particularly when the overall number of columns is equal or smaller than eight, as in most practical small scale HPLC-SMB applications. As a matter of fact it has been demonstrated that SMB profiles approach TCC ones for large number of subsections per section and that for a small number of columns the two profiles can be significantly different.

In the following for the study case considered, the region of complete separation in the $(m_2, m_3)$ plane in the presence of axial dispersion is drawn and compared with the one provided by the Equilibrium Theory. The model system chosen is the separation of the enantiomers of 1,1'-bi-2-naphtol on a 3,5-dinitrobenzoyl phenylglycine bonded to silica gel stationary phase, using a mixture of heptane-hexane (78:22) as mobile phase. The adsorption equilibrium is described by the bi-Langmuir isotherm whose parameters are given in Figure 2. It follows that A denotes the more retained enantiomer and B the less retained one. The separation is carried out in a 8-column SMB unit with a 2-2-2-2 configuration, such as the one shown in Figure 1; the column volume is $V = 55.75 \text{ cm}^3$ and the overall void fraction $\varepsilon = 0.4$. For this system we have used an axial dispersive model with $N_{pad} = 30$; the model has been compared with the more detailed solid linear driving force model and similar results have been obtained, thus suggesting that the simpler model is suitable for the following analysis.

It is worth noting that this approach, which is based on numerical calculations, may be applied also to isotherms for which the Equilibrium Theory solution is not available at all. An analysis of the performances of the unit when the operating point crosses the region of separation is reported; an asymmetric behavior is observed when only one stream has to be collected pure. This finding is rather important in applications since it allows to optimize the separation when only one of the compounds is needed pure. Finally, some experimental data are discussed in the light of the theoretical results obtained, in order to assess their reliability and practical relevance.

### 4.1 Region of complete separation

In the framework of Equilibrium Theory the optimal operating conditions for SMBs are obtained by calculating the region of complete separation in the $(m_2, m_3)$ plane. This region is made up of operating points leading to complete separation, i.e. both components are collected pure in the product streams, provided that proper constraints on the parameters of the regenerating sections $m_1$ and $m_4$ are fulfilled. These are simply given by a lower bound for $m_1$ and an upper bound for $m_4$, corresponding to the specific tasks of section
1 and 4, i.e. the regeneration of the eluent and of the adsorbent, respectively. The aim of this section is to determine the complete separation region in the \((m_2, m_3)\) plane in the presence of dispersive effects, i.e. using the equilibrium-dispersive model introduced in the previous section. Since sections 2 and 3 are the heart of the separation, in the following we concentrate on the \((m_2, m_3)\) plane and select the operating conditions for parameters \(m_1\) and \(m_4\) far enough from their respective critical values. In such a way, we are guaranteed that the results obtained for sections 2 and 3 are not affected by any improper operation of the regenerating sections 1 and 4.

The objective of this analysis is to draw conclusions of general validity about the effect of dispersive phenomena on SMB performances. This is conventionally done by using a case study to illustrate the various findings. In particular, we have selected the separation of the enantiomers of bi-naphtol referred to in the previous section. In all the following simulations a few parameters have been held constant: column volume \(V = 55.75\) cm\(^3\); overall void fraction \(\varepsilon = 0.4\); switch time \(t^* = 170\) s; flow rates \(Q_1 = 78.7\) cm\(^3\)/min, i.e., \(m_1 = 6\), and \(Q_4 = 19.7\) cm\(^3\)/min, i.e., \(m_4 = 1\); feed concentration \(c_A^R = c_B^R = 2.9\) g/l. This choice of the parameters \(m_1\) and \(m_4\) guarantees complete regeneration of stationary and mobile phases in sections 1 and 4, respectively. We will come back to these constraints in the discussion of the experimental results in order to analyse their effect on the separation performances. In all simulations cyclic steady-state conditions have been reached, as confirmed by overall and single component mass balances.

In Figure 4.1, the results obtained by assuming an apparent axial dispersion corresponding to \(N_p = 30\) are illustrated. In particular, the contour lines of the purities in the outlet streams, obtained by performing simulations on a square grid in the \((m_2, m_3)\) plane spaced by \(\Delta m = 0.025\), are drawn. Contour lines for the purity in the raffinate, \(P_R\), intersect the diagonal on the top right corner of the diagram; the region below each specific \(P_R\) contour line, i.e. between this and the diagonal, corresponds to operating conditions leading to a purity in the raffinate larger than the value labelling the line itself (e.g., 99\% for the lowest thick solid curve). Contour lines for purity in the extract, \(P_E\), intersect the diagonal on the bottom left corner of the diagram; the region above and on the right hand side of a specific \(P_E\) contour line is constituted of operating points leading to a purity in the extract larger than the value corresponding to the line itself.

Based on these definitions, it is possible to readily identify all the operating conditions leading to purity values in extract and raffinate larger than any given pair of values. For instance, the triangle-shaped region whose boundaries are the diagonal and the two thick solid contour lines corresponding to \(P_E = 99\%\) and \(P_R = 99\%\) identifies operating conditions
achieving 99% purity or more in both product streams. The vertex of this region, i.e., the furthest point from the diagonal, corresponds to optimal operating conditions in terms of productivity and eluent consumption when dispersive effects are accounted for.\cite{ref37} The results illustrated in Figure 4.1 allow one to choose the optimal operating conditions for the SMB separation fulfilling any process requirement, in terms of purity of the outlet streams. Once the values of the $m_j$ parameters have been chosen in this way, the specific values of flow rates to be selected can be calculated using Eq. (1.7). To this aim, a further constraint to select a proper value of $t^*$ must be enforced; this may be done by requiring that either column efficiency is large enough or pressure drop is small enough, or else by imposing a given value for the overall feed flow rate.

The effect of changes in column efficiency is illustrated in Figure 4.2. Here, the same region corresponding to $P_E$ and $P_R$ values larger than 99% as in Figure 4.1 is shown (broken boundaries), together with the region calculated in the same way but with a lower column efficiency, namely with $N_p = 20$ (dash-dotted boundaries). It can be redily observed that reducing column efficiency makes the region of the operating parameter plane where the desired purity values are achieved (99% in this example) smaller. For a comparison, in Figure 4.2 the ideal complete separation region (solid boundaries) corresponding to the isotherms (2.21) and calculated in the frame of Equilibrium Theory,\cite{ref38} i.e., assuming $N_p \to \infty$, is
Figure 4.2: The region of complete separation, calculated through Equilibrium Theory assuming an infinite column efficiency (—.) is compared with the region where the purity of both extract and raffinate is greater than 99% assuming an efficiency of 30 (---) and 20 (---) theoretical stages. The vertex \( w \) of the region obtained through Equilibrium Theory is the ideal optimal operating point.\(^\text{37}\)

It is seen that the separation region corresponding to finite columnn efficiency, approaches the ideal region given by Equilibrium Theory solution when \( N_p \) increases. In particular this applies to the optimal operating points, i.e. the vertices of the regions drawn in Figure 4.2. Moreover it can be noted that even with \( N_p = 30 \), i.e. with a rather low column efficiency compared to the typical experimental, the vertex of the 99\% purity region is very close to the optimal point of the ideal complete separation region calculated without dispersive effects, which leads to 100\% purity.

Finally, let us consider Figure 4.3 where the extract and raffinate purity are plotted as a function of the number of theoretical plates. The same operating conditions, corresponding to the optimal point of the ideal complete separation region in Figure 4.2, i.e., \( m_2 = 2.49 \) and \( m_3 = 3.14 \), but different column efficiencies have been adopted. This corresponds to different \( N_p \) values, i.e., to different number of space discretisation points. It is seen that the complete separation prediction of Equilibrium Theory is reached very rapidly for the raffinate (at \( N_p \approx 50 \)) and a bit slower for the extract. However, it is noteworthy that in both cases very high purity values (above 99\%) in both streams are achieved at relatively low efficiency values (\( N_p \approx 40 \)). The same pattern of behavior, i.e., a first fast improvement
Figure 4.3: extract and raffinate purity as function of the number of theoretical stages. The simulations are performed in the ideal optimal operating point w shown in Figure 4.2; the corresponding operating conditions are \( m_2 = 2.49 \) and \( m_3 = 3.14 \).

of performances while increasing column efficiency at low values of \( N_p \) followed by a slow asymptotical attainment of the ideal dispersion-free performances, is typical for SMB units under overload conditions and not only for the specific system used for the calculations above. In particular the same qualitative behavior is exhibited also by non-langmuirian systems for which the Equilibrium Theory analysis is not feasible.

A similar analysis of the effect of dispersive phenomena on SMB behaviour has been reported by Rodrigues and co-workers,\textsuperscript{13,14} who have also investigated experimentally the system used above as a case study. Their results (see Figures 2, 3, 6 and 7 in\textsuperscript{13}) are qualitatively similar to ours, as illustrated in Figures 4.1 and 4.2, but quantitatively different for at least two reasons. First, they use a TMB model which accounts for both axial dispersion and mass transfer resistance; though in principle under the same conditions the two models should produce the same results, it is not easy to tune the different parameters in the two models in order to make them match exactly. Secondly, in the analysis by Rodrigues and co-workers the overall product flow rate, i.e. the sum of the flow rates of extract and raffinate, has been kept constant together with the value of \( m_4 \). This implies that in all their calculations, \( m_1 \) is a linear function of \( m_2 \) and \( m_3 \), namely \( m_1 = 4.76 - m_3 + m_2 \), and not a constant as in our calculations. It follows that the separation regions shown in\textsuperscript{13} are made of points which do not fulfil always the key constraints on the flow rate ratios in section 1 and 4. This applies
in particular to the regions where complete separation is not achieved; in fact, the shape of these regions in our Figure 4.1 is completely different from that reported in\textsuperscript{13,14} Even though their choice is legitimate, we believe that when representing operating regions in the \((m_2, m_3)\) plane it is better to guarantee that the constraints on \(m_1\) and \(m_4\) are fulfilled, so that the picture that one obtains is more general and clear.

4.2 Performance parameters

The operating parameter space of SMB units is multidimensional. Experimental and numerical results of SMB performances are usually performed along a one-dimensional subset of the whole space, with the aim of locating the complete separation region or determining the optimal operating conditions with respect to a single operating parameter. In this section, we revise a number of these strategies focusing on the effect of dispersive phenomena on process optimization. In order to quantitatively determine the performance of a separation process let us introduce the following parameters: purity of the product streams, defined as:

\[
P_E = \frac{c_A^E}{c_A^E + c_B^E} \cdot 100
\]  

\[
P_R = \frac{c_B^R}{c_A^R + c_B^R} \cdot 100;
\]

and specific productivity with respect to the species collected pure in the relevant outlet stream (this is of particular importance whenever only one of the components to be separated is of interest\textsuperscript{37}):

\[
PR_A = \frac{Q_E c_A^E}{n_e V}
\]

\[
PR_B = \frac{Q_R c_B^R}{n_e V}
\]

The different strategies considered in the following are illustrated in Figure 4.4, where the complete separation region in the \((m_2, m_3)\) plane for the case study considered in the previous section as calculated through Equilibrium Theory is shown, together with the other regions of partial separation (i.e., only pure extract, only pure raffinate and no pure outlet streams). In particular, four sets of operating points are considered, each corresponding to
Figure 4.4: regions of separation in the \((m_2, m_3)\) plane at \(c_A^R = c_B^R = 2.9\) g/l. The simulations are carried out moving the operating point along the straight lines \(AB, CD, EF, GE\), while keeping all the other parameters constant. The corresponding flow rate values for \(Q_2\) and \(Q_3\) can be obtained from Eq. (1.7).

a straight segment in the \((m_2, m_3)\) plane. The same parameters as in the previous section are held constant.

First, let us consider the operating points \(A \rightarrow B\) on a segment parallel to the diagonal. In practice these conditions are obtained by changing the extract and raffinate flow rates by the same quantity but in opposite direction, so as to keep constant the feed and eluent flow rates. This strategy has been adopted for example by Francotte and Richert\(^{11,45}\) in their experimental investigation of the guaifenesine separation. A similar situation occurs when all the flow rates are kept constant and the switching time is changed. In this case the obtained set of operating points lies on a straight line which is almost parallel to the diagonal, as for the experimental results reported by Pais et al\(^{13,14}\) and Pedeferri et al.\(^{16}\)

In Figure 4.5 the calculated purities in the outlet streams as a function of the \(m_2\) value are shown, when the dispersive effects correspond to \(N_p = 30\). It appears that dispersive effects reduce the complete separation region which Equilibrium Theory predicts for \(m_2\) values between 2.54 and 2.72, to a very small neighborhood of the value \(m_2 = 2.68\). It is worth noting that the dispersive complete separation region is very small in this case because the segment AB crosses the ideal complete separation region at a location where this is rather narrow, i.e. very close to the ideal optimal operating point represented by the vertex of the
4.2 Performance parameters

Equilibrium Theory region. When considering the set of operating points C→D in Figure 6, which are further away from the optimal point, then both the ideal and the dispersive complete separation regions are larger. This is confirmed by the purity values shown in Figure 4.6 corresponding to operating points along the segment C→D, with \( N_p = 30 \). In the same figure the results obtained with a lower column efficiency, i.e. \( N_p = 20 \), are also shown. As expected from the results shown in Figure 4.2, the range of \( m_2 \) values achieving complete separation is smaller than in the case of \( N_p = 30 \). It is worth noting that on the one hand extract purity at \( N_p = 20 \) is always smaller than at \( N_p = 30 \), while on the other hand raffinate purity exhibits a crossover behaviour for \( m_2 \) larger than about 3.15. This is somehow unexpected, even though its importance should not be overestimated since this phenomenon occurs for operating conditions where raffinate purity is rather poor (less than 90%), hence not very interesting from the application viewpoint. Finally note that for both sets of points A→B and C→D the purity performances illustrated in Figures 4.4 and 4.5 are consistent with the position of each operating point in the \((m_2, m_3)\) parameter plane shown in Figure 4.4. In particular, as \( m_2 \) and \( m_3 \) increase, first 100% purity in the raffinate and low purity in the extract are observed (pure raffinate region); then, both streams achieve 100% purity (complete separation region), and finally \( P_E \) is 100% and the raffinate purity is lost (pure extract region).

The third set of operating points considered, i.e. E→F in Figure 4.4, is obtained by in-
Figure 4.6: extract and raffinate purity as function of \( m_2 \) in the set of simulations CD of Figure 6. The column efficiency is 30 (—) and 20 (- -) theoretical stages.

Increasing the feed flow rate and the raffinate flow rate by the same amount (keeping all the other flow rates constant) and was adopted by Francotte and Richert\textsuperscript{11,45} to improve the productivity of the unit with respect to the component collected pure in the extract. The purity performances in the case of \( N_p = 30 \) are reported in Figure 4.7 as a function of \( m_3 \), together with the productivity parameter \( P_{RA} \) defined by Eq. (4.3). The purity values are consistent with the position of the operating points in the \((m_2, m_3)\) parameter plane, which are first inside the complete separation region and then move to the pure extract region. Therefore, \( P_E = 100\% \) in all cases whereas \( P_R \) drops below 100\% for \( m_3 \) larger than 3.25, i.e. a bit earlier then predicted by Equilibrium Theory \( (m_3 = 3.27) \). The behaviour exhibited by \( P_{RA} \) is rather interesting and indicates that when entering the pure extract region, the extract purity remains 100\%, but no further improvement of the productivity of the species collected in the extract is possible. In other words, in these conditions all the additional amount of A fed to the unit is directly conveyed to the raffinate outlet.

A different behavior is observed if, starting from the operating point E, the segment E→G is followed (see Figure 4.4). From the practical point of view this corresponds to the simultaneous increase of the feed and extract flow rates, while the other streams are left unchanged. With reference to Figure 4.8, where the results corresponding to \( N_p = 30 \) are illustrated, it can be seen that as \( m_2 \) decreases we go from an operation where both extract and raffinate are pure to one where the raffinate purity remains 100\% while that in the extract
Figure 4.7: performance parameters along the set of points EF in Figure 6 as function of the operating parameter $m_3$. The purity of the extract $P_E$ and of the raffinate $P_R$ are drawn, as well as the normalized value of the productivity of A.

decreases. This is consistent with the transition from complete separation to pure raffinate region shown in Figure 4.4. However, when compared to the raffinate purity behavior in Figure 4.7, it is found that the extract purity drops earlier with respect to the critical ideal value $m_2 = 2.57$. This is consistent with the results shown in Figure 4.2, where it appears that the dispersive effects strongly bend the left-hand side of the complete separation region, i.e. the region of pure raffinate expands rightwards with respect to the ideal case. Another difference with respect to the previous case, which has even more relevant practical implications, is that the productivity of B defined by Eq. (4.4) increases steadily while $m_2$ decreases, i.e. the feed flow rate increases. This means that, moving leftwards along segment EG or along other lines parallel to the horizontal axis allows to increase the productivity of the species collected in the raffinate, while keeping its purity equal to 100%. This indicates that separations where we are interested in the recovery of only one pure component exhibit a rather asymmetric behavior depending on whether such a component is recovered in the extract or in the raffinate. In the first case there is an upper bound in the feed flow rate above which the productivity of the pure component does not increase. In the second case such a bound does not exist and it is possible by increasing the feed flow rate continuously to improve the productivity of the pure component. Of course, when doing this, the process yield, i.e. the fraction of pure component in the raffinate with respect to the total feed
amount, continuously decreases. The above mentioned asymmetrical behavior is obviously quite relevant when designing a separation process. Its nature is actually not related to dispersive phenomena, but only to the countercurrent flow of the two phases and to the phase equilibria. This phenomenon can be in fact explained using Equilibrium Theory. Here it suffices to say that the bi-Langmuir isotherm, as well as the Langmuir isotherm, exhibits a watershed point in the phase plane spanned by the concentrations of the two species to be separated. In the frame of Equilibrium Theory, this is located on the $c_A$ axis and represents the unique composition state where the two characteristic lines emanating from each point in the $(c_A, c_B)$ plane coincide. From the practical point of view, its $c_A$ concentration value represents the maximum value of the concentration of $A$ achievable in the second section of the SMB unit, whatever the feed concentration $c_A^F$ is. Since no similar constraint exists for the less retained species $B$, it follows that the $c_A^F$ value, hence $PR_A$ from Eq. (4.3), is upper bounded, while on the other hand $c_B^R$, hence $PR_B$ from Eq. (4.4), can reach any value.

Figure 4.8: performance parameters along the set of points GE in Figure 6 as a function of the operating parameter $m_2$. The purity of the extract $P_E$ and of the raffinate $P_R$ are drawn, as well as the normalized value of the productivity of $B$. 
4.3 Comparison with experimental data

In this section the above theoretical findings are used to discuss and explain a set of experimental results reported by Pais et al.\textsuperscript{13,14} This is possible because the bi-Langmuir isotherm which describes the adsorption thermodynamics of this system has been used in all previous calculations. The characteristics of the experimental system and the SMB unit have been already discussed in section 5.3. The experimental operating conditions in terms of $m_2$ values and switching time $t^*$, are summarized in Table 4.1, while the corresponding operating points are shown in Figure 4.2, where their position can be compared with the complete separation region calculated through Equilibrium Theory and the 99% purity regions obtained for $N_p = 20$ and $N_p = 30$.

It is worth noting that runs A, B, C and D have been performed with the same fluid flow rates for all SMB streams, but increasing values of the switching time $t^*$. On the other hand, run B', which shares the same operating point as run B in the $(m_2, m_3)$ plane, has been performed with smaller flowrate values and a larger $t^*$ than run B, so as to obtain a better column efficiency. In order to understand the unit behavior in these different operating conditions, we should consider that by changing the switching time value at constant flow rates, not only $m_2$ and $m_3$ change in such a way that the complete separation region is crossed (see Figure 4), but also $m_1$ and $m_4$ change according to Eq. (1.7). Therefore a careful check of the values of those parameters with respect to the corresponding critical values is necessary in order to guarantee that the regenerating sections of the SMB operate properly. To this aim in Table 4.1 the critical values of $m_1$ and $m_4$ are reported, as calculated using the adsorption isotherm (2.21). The experimental separation performances are reported in Table 4.2, together with those calculated using the equilibrium-dispersive model considering rather low efficiency columns, i.e. $N_p = 20$ and $N_p = 30$.

<table>
<thead>
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<th>Run</th>
<th>$(m_{1,cr})$</th>
<th>$m_1$</th>
<th>$m_2$</th>
<th>$m_3$</th>
<th>$m_4$</th>
<th>$(m_{4,cr})$</th>
<th>$t^*$ sec</th>
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<td>4.01</td>
<td>2.69</td>
<td>2.99</td>
<td>2.24</td>
<td>2.56</td>
<td>165</td>
</tr>
<tr>
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<td>4.20</td>
<td>2.69</td>
<td>3.00</td>
<td>2.39</td>
<td>2.55</td>
<td>172</td>
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<tr>
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<td>2.56</td>
<td>2.63</td>
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</tr>
</tbody>
</table>

Table 4.1: values for the $m_j$ parameters taken from\textsuperscript{13,14} and critical values for $m_1$ and $m_4$ as obtained through Equilibrium Theory. The position of the operating points in the $(m_2, m_3)$ plane is shown in Figure 4.2.
First, let us consider runs A, B, C and D. It is readily seen that in no experiment complete separation has been achieved even though the complete separation region is indeed crossed when going from point A to point D in Figure 4.2. However, this inconsistency is only apparent and can be explained by considering the performances of sections 1 and 4. Let us consider the raffinate purity. This should be the highest in run A which is in the pure raffinate region. On the contrary experimental value is relatively low, i.e. 93%, and is qualitatively consistent with the calculated value which is about 95%. This can be explained by noting that the parameter $m_1$ (cf. Table 4.1) is smaller than the critical value and therefore the position of the operating point in the $(m_2, m_3)$ plane is not sufficient anymore to define the unit performances. In this case in fact, although sections 2 and 3 properly perform their task, section 1 does not achieve complete regeneration of the stationary phase. Therefore, some of the more retained component is kept by the stationary phase when the switch occurs and it is carried to the raffinate outlet, thus spoiling its purity (see Mazzotti et al.\textsuperscript{35} for a similar effect in the case of the separation of linear and nonlinear paraffins).

The poor raffinate purity in run A is not due to dispersive effects. This point can be best demonstrated by a simple numerical experiment, whose results are reported in Tables 4.3 and 4.4. The first one reports the operating conditions adopted in the simulations and the second one the calculated purity performances, corresponding to $N_p = 20$ and $N_p = 30$. Operating conditions for the calculations are chosen in such a way that the $m_2$ and $m_3$ values are the same as in the experimental runs, whereas $m_1$ and $m_4$ fulfill the corresponding constraint with a 20% margin (cf. Tables 4.1 and 4.3). In this case it is found for run A that for both column efficiencies, 99.9% purity in the raffinate is achieved.

The same considerations, as far as the raffinate purity is considered, apply also to runs B and C, where the experimental value of $m_1$ is very close to the critical value. In run D the adsorbent regeneration is likely to be complete since the experimental value of $m_1$ is

<table>
<thead>
<tr>
<th>Run</th>
<th>Experimental purity</th>
<th>$N_p = 20$</th>
<th>$N_p = 30$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$P_E$</td>
<td>$P_R$</td>
<td>$P_E$</td>
</tr>
<tr>
<td>A</td>
<td>74.0</td>
<td>93.0</td>
<td>81.7</td>
</tr>
<tr>
<td>B</td>
<td>93.0</td>
<td>96.2</td>
<td>98.2</td>
</tr>
<tr>
<td>B'</td>
<td>94.5</td>
<td>98.9</td>
<td>98.3</td>
</tr>
<tr>
<td>C</td>
<td>95.6</td>
<td>95.4</td>
<td>99.2</td>
</tr>
<tr>
<td>D</td>
<td>91.5</td>
<td>70.9</td>
<td>99.2</td>
</tr>
</tbody>
</table>

Table 4.2: purity values and results of the simulations for the operating conditions in Table 4.1.
Table 4.3: values of the $m_1$ and $m_4$ parameters to guarantee regeneration in section 1 and 4. The position of the operating points in the $(m_2, m_3)$ plane is the same as reported in Table 4.1.

<table>
<thead>
<tr>
<th>Run</th>
<th>$m_1 (= 1.2 \cdot m_{1,cr})$</th>
<th>$m_2$</th>
<th>$m_3$</th>
<th>$m_4 (= 0.8 \cdot m_{4,cr})$</th>
<th>$t^* \text{ sec}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>4.84</td>
<td>2.45</td>
<td>2.72</td>
<td>1.97</td>
<td>153</td>
</tr>
<tr>
<td>B</td>
<td>4.84</td>
<td>2.69</td>
<td>2.99</td>
<td>2.05</td>
<td>165</td>
</tr>
<tr>
<td>B'</td>
<td>4.84</td>
<td>2.69</td>
<td>3.00</td>
<td>2.04</td>
<td>172</td>
</tr>
<tr>
<td>C</td>
<td>4.84</td>
<td>2.75</td>
<td>3.05</td>
<td>2.06</td>
<td>168</td>
</tr>
<tr>
<td>D</td>
<td>4.84</td>
<td>3.06</td>
<td>3.39</td>
<td>2.10</td>
<td>183</td>
</tr>
</tbody>
</table>

Table 4.4: results of the simulations for the conditions reported in Table 4.3.

<table>
<thead>
<tr>
<th>Run</th>
<th>$N_p = 20$</th>
<th></th>
<th>$N_p = 30$</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$P_E$</td>
<td>$P_R$</td>
<td>$P_E$</td>
<td>$P_R$</td>
</tr>
<tr>
<td>A</td>
<td>81.3</td>
<td>99.9</td>
<td>83.9</td>
<td>99.9</td>
</tr>
<tr>
<td>B</td>
<td>98.1</td>
<td>99.9</td>
<td>99.2</td>
<td>99.9</td>
</tr>
<tr>
<td>B'</td>
<td>98.2</td>
<td>99.9</td>
<td>99.3</td>
<td>99.9</td>
</tr>
<tr>
<td>C</td>
<td>99.1</td>
<td>99.9</td>
<td>99.8</td>
<td>99.9</td>
</tr>
<tr>
<td>D</td>
<td>99.9</td>
<td>85.8</td>
<td>99.9</td>
<td>85.3</td>
</tr>
</tbody>
</table>

about 10% larger than $m_{1,cr}$. However in this case the raffinate purity is actually the lowest because the values selected for $m_2$ and $m_3$ correspond to high purity only in the extract, as shown in Figure 4.2. Accordingly, in all simulations of run D with different $m_1$ values (see Tables 2 and 4), but always larger than $m_{1,cr}$, the raffinate purity is very low, i.e. about 85.5%. The conclusion is that the behavior of this unit, with respect to the raffinate, is qualitatively determined by the choice of the parameters $m_1$ and $m_4$, while dispersive effects are relevant only for the quantitative values of the performances parameters. This clearly appears from the results in Table 4.4 indicating that once the parameters $m_1$ and $m_4$ are properly selected, the calculated performances are in full agreement with the positions of the operating points in the $(m_2, m_3)$ plane in Figure 4.2.

The interpretation of the experimental results becomes less clear when we consider the extract purity achieved in runs A, B, C and D. Indeed the very low experimental value of $P_E$ in run A, 74%, is consistent with the position of the operating point in the pure raffinate region and with all calculated values reported in Tables 2 and 4, which are between 81% and 84%. However, in the other three operating conditions higher purity values in the
extract should be expected. This is in fact what is found with the equilibrium-dispersive model simulations reported in Table 2, which predict in all cases larger purity values for the extract. One possible explanation for this disagreement is that the \( m_4 \) value is smaller than the critical value \( m_{4,c} \) (see Table 1) but only with a very small margin, i.e. about 12%, 12% and 3% for runs B, C and D, respectively. Thus, small inaccuracies in the experimental variables which affect the behavior of the section could lead to an incomplete regeneration of the mobile phase which through recycle would carry some amount of compound B in section 1, thus polluting the extract. Note that this observation applies particularly to run D, which is the one where the highest extract purity should be expected. On the other hand for runs B and C there is another aspect which is worth considering. These points are in fact close to the left boundary of the ideal complete separation region and this zone of the \( (m_2, m_3) \) plane is rather sensitive to the column efficiency as illustrated in Figure 4.2. Therefore, it is useful to consider the position of the operating points in the \( (m_2, m_3) \) plane with respect to the 99% regions calculated with different number of theoretical plates and shown in Figure 4.2. It can be observed that experimental values of \( P_e \) less than 96% in run B and C can be explained also by assuming that the column efficiency does not correspond to \( N_p = 30 \), but it is close to or even less than \( N_p = 20 \).

Finally, let us consider run B' and compare it to run B. The qualitative behavior is similar, i.e. low extract purity and larger, although not very high, raffinate purity. The experimental \( m_1 \) value in this run has been chosen 5% greater than the critical value and thus a better regeneration of the solid phase is fulfilled. According to the previous analysis the raffinate purity achieved, 98.9%, is much higher than in run B. Moreover, from the quantitative point of view, separation performances are better in the case of run B', also because the switching time is larger and the flow rates are smaller. This implies that the improvement in terms of purity of the outlet streams is compensated by a lower productivity. The effect of the increase of the \( m_1 \) value is observed by considering the calculated performances for runs B and B' (see Table 4.2).
Chapter 5

Experimental analysis of SMB performance under nonlinear conditions

*The scale-up of enantiomer separations from the batch to the continuous Simulated Moving Bed process is often an important step in the development and production of a new product in the fine chemical and pharmaceutical industry. In the last years, the SMB technology has shown many advantages over batch preparative chromatography and attracted the interest of the fine chemical industry.2,10–12,80

The key to the success of this unit operation rests on its flexibility and fast scale-up. The same SMB unit (equipped with the same or different columns) can be used in fact for many separations allowing the parallel screening of many potential drug candidates. Moreover, under linear conditions the scale-up of the separation from the HPLC to the SMB is rather straightforward.16,72 This allows the time to develop a new product to be shortened and therefore the corresponding patents to be exploited for a longer time.

On the other hand, the scale-up of separations under nonlinear conditions is more difficult and may require a lengthy trial and error procedure.45,80,81 However, higher productivity and lower desorbent requirement per unit mass of product motivate this pursuit. A reliable design of the non-linear separation based on detailed6,13,32,82 or ideal models16,45 is possible but it requires the knowledge of the adsorption equilibria. The determination of such equilibria is time consuming and in addition it depends on the availability of large amounts of pure substances and therefore it may not be feasible in the early development of a new product, particularly in the pharmaceutical industry.

The aim of this chapter is twofold. On the one hand, a short-cut design method for the design

*In collaboration with GianMarco Zenoni, Laboratory of Technical Chemistry ETH
of nonlinear separations based on the Equilibrium Theory model is presented. This approach is different from solutions presented earlier which make use either of adsorption/desorption or pulse experiments. This solution aims at finding the approximate solution of the Equilibrium Theory model using both breakthrough and pulse experiments designed to minimize the amount of pure products needed. The experimental procedure is applied to a model system: the separation of the Tröger's base enantiomers on microcrystalline triacetate cellulose (CTA). This procedure is designed for the situation where, having already realized the SMB unit, one would like to use it for a new separation. This is a typical situation for multipurpose units in the types of industries mentioned above. On the other hand, we study the effect of the feed concentration on the separation performance of the SMB, which is of course the main source of nonlinearity in these systems. The experimental SMB results are discussed in the light of the theoretical understanding of SMB behavior and the deviations from the ideal behavior due to mass transfer resistance and extracolumn band broadening are assessed.

5.1 Experimental set-up

5.1.1 Columns and Chemicals

Unsupported microcrystalline cellulose triacetate beads in the size range 15-25 μm (Merck 16362) were packed in a stainless steel chromatographic column (0.46 cm I.D. x 25 cm). Some pulse experiments were carried out in a shorter column (0.46 cm I.D. x 5 cm). The stationary phase has been boiled in pure ethanol for 30 minutes to let it swell. The suspension was packed at room temperature under a pressure of 200 bar with ethanol as a pushing solvent at a flow rate of 4 cm³/min. The pure (-)-TB and (+)-TB enantiomers have been purchased from Aldrich; all binary mixtures have been prepared by properly mixing the pure enantiomers. Pure ethanol used as mobile phase as well as 1,3,5-tri-ter-butylbenzene (TTBB) used to measure the column porosity, have been purchased from Fluka and used as received. The purity of the Tröger's base used in the experiments is 99%.

5.1.2 Analytical methods

The analysis is performed under isocratic conditions on an HP 1100 liquid chromatograph equipped with a quaternary pump, an autosampler and a thermostatted column compartment kept at 65 °C. The flow rate is kept constant at the value of 0.5 cm³/min. The
5.1 Experimental set-up

The SMB unit has the open-loop 2-2-2-2 configuration, shown in Figure 5.1.\(^\text{16}\) The columns are located in a thermostatted chamber which is kept at a temperature of 65 °C using a proper control scheme. Four flows (desorvent, extract, feed and raffinate) are controlled by 4 HPLC pumps (Jasco PU-987). An on-line measurement of the weight of the feed and the product vessels (Mettler-Toledo 8700) allows to cross-check the flow rates. The flows among the columns in the unit are managed by 5 (12+1)-port multiposition valves (Vici-Valco EMT-6-CSD12UW) connected to each of the eight columns. The distribution of extracolumn dead volumes is uneven, namely: \(V_1^D = 1.21\text{ cm}^3\), \(V_2^D = 2.30\text{ cm}^3\), \(V_3^D = 1.21\text{ cm}^3\), \(V_4^D = 1.76\text{ cm}^3\).\(^\text{16}\) During SMB runs steady state conditions have been considered to be attained when mass balances were fulfilled within a 3% maximum error.

Figure 5.1: the scheme of the SMB pilot unit: 8 columns, 2-2-2-2 configuration. The loop in open between section 4 and section 1.
5.2 Design of operating conditions

Before presenting the experimental short-cut design procedure, let us briefly summarize the criteria for the design of SMB separations under ideal conditions, i.e. neglecting axial dispersion and mass transfer resistance. In this framework, i.e. Equilibrium Theory, the separation performance depends on the generalized flow rate ratios $\bar{m}_j$ in the four sections of the unit:

$$\bar{m}_j = \frac{Q_j t^* - V \varepsilon^* - V_j^D}{V (1 - \varepsilon^*)}$$

where all symbols are defined in the Notation section. This definition accounts for the effect of extracolumn dead volume and depends on the geometric properties of the SMB (column volume $V$, extracolumn dead volume $V_j^D$ and overall void fraction $\varepsilon^*$), the switch time $t^*$ and the flow rate $Q_j$ in every section of the unit. The solution of the Equilibrium Theory model allows to calculate the region of complete separation in the $(\bar{m}_2, \bar{m}_3)$ plane (see Figure 5.2) and the constraints on the regenerating sections when the multicomponent equilibria are described with a linear, stoichiometric and non stoichiometric Langmuir, bi-Langmuir or IAS model. If regeneration of the stationary and fluid phases is achieved in sections 1 and 4, complete separation is attained for the operating points belonging to the triangle shaped region in the $(\bar{m}_2, \bar{m}_3)$ plane in Figure 5.2.

Under linear conditions the adsorbed amount is proportional to the fluid phase concentration, i.e. $q_i = H_i c_i$. The following constraints must be fulfilled:

- section 1 : $H_A \leq \bar{m}_1 \leq \infty$
- section 2 : $H_B \leq \bar{m}_2 \leq H_A$
- section 3 : $H_B \leq \bar{m}_3 \leq H_A$
- section 4 : $\frac{\varepsilon_p}{\varepsilon_p - 1} \leq \bar{m}_4 \leq H_B$

whose projection on the $(\bar{m}_2, \bar{m}_3)$ plane defines the triangular separation region in Figure 1 (region 1). The coordinates of the points a and b along the diagonal are given by the Henry constants of the more and less retained enantiomer, i.e. $H_A$ and $H_B$ (here and in the following A denotes the more retained component). The Henry constants are usually determined from the retention times of a small racemic pulse, $t_i^R$:

$$H_i = \frac{(t_i^R - t_0)}{t_0} \frac{\varepsilon^*}{1 - \varepsilon^*}$$

where $t_0$ is the residence time of an inert tracer and the overall void fraction is given by:

$$\varepsilon^* = \frac{t_0 Q}{V}.$$
Figure 5.2: effect of the feed concentration on the complete separation regions in the \((\bar{m}_2, \bar{m}_3)\) plane for a bi-Langmuir isotherm. Infinite dilution \(c_F^0 \to 0\) (region 1), \(c_F^0 = 1.4\) g/l (region 2) and \(c_F^0 = 5.8\) g/l (region 3). The short-cut separation region bounded by \(bb'\) and \(aa'\) approximates the region of complete separation calculated rigorously with Equilibrium Theory.

5.2.1 Short-cut approach

Under nonlinear conditions the shape of the separation region depends on the feed concentration and on the multicomponent adsorption equilibria. Accordingly, different isotherm models lead to separation regions of different shapes, even though under dilute condition they all converge to the same linear adsorption isotherm. As an example, the region of complete separation for a bi-Langmuir isotherm is shown in Figure 5.2. As the feed concentration approaches zero, i.e. when \(c_F^0 \to 0\), the bi-Langmuir model converges to the linear model and therefore the region of separation is the square triangle (region 1) defined by Eqs (5.3) to (5.4). As the feed concentration increases the vertex of the triangle, which is the point where the highest productivity is achieved, moves to smaller \(\bar{m}_2\) and \(\bar{m}_3\) values and gets closer to the diagonal (see regions 2 and 3 in Figure 5.2). Such a deformation of the complete separation region is the result of the nonlinear competitive adsorption equilibria.

The objective of this section is to estimate through a simple experimental procedure the region bounded by the curve \(bw'\) and the curve \(aw'\) which approximates the complete separation region obtained as a rigorous theoretical solution of the Equilibrium Theory model. Here \(w'\) is the point of intersection of the curves \(bb'\) and \(aa'\) and represents an
approximation of the optimal point of the complete separation region.

In the following we assume that the system exhibits a competitive adsorption behavior and that the transitions occurring during column adsorption and desorption experiments, are shocks and waves, respectively. These are rather general assumptions that apply to a large number of systems of interest (cfr.41 for a thorough discussion about this point). In order to reduce the amount of experimental information needed, the curves bb' and aa' (see Figure 5.2) are approximated with straight lines and therefore only one point along these line is calculated (a' and b'), the other two points along the diagonal being the Henry constants (a and b).

The approximate region of complete separation corresponding to a mixture of feed composition \((c_A^F, c_B^F)\) is then bounded by the following two straight lines:

- straight line aa'. The coordinates of point a' are given by:

\[
\bar{m}_2 = \frac{n_B(c_A^F, c_B^F)}{c_B^F} \quad \bar{m}_3 = \frac{n_A(c_A^F, c_B^F)}{c_A^F}
\] (5.8)

which require the knowledge of the amount of A and B adsorbed at equilibrium with the liquid at the feed concentration \((c_A, c_B)\). This can be readily estimated through a binary frontal experiment with the feed mixture during which the outlet concentration profiles of the two species are monitored, for example using the on-line system described elsewhere.85

- straight line bb'. The coordinates of point b' are given by:

\[
\bar{m}_2 = \frac{\partial n_B}{\partial c_B} \bigg|_{(c_A^*, 0)} = \left( \frac{t_B^* Q}{V} - \varepsilon^* \right) \frac{1}{1 - \varepsilon^*}
\]

\[
\bar{m}_3 = \bar{m}_2 + \frac{q_A(c_A^*, 0) - \bar{m}_2 c_A^F}{c_A^F}
\] (5.10)

where \(t_B^*\) is the retention time of the less retained species after a small racemic pulse has been injected in a column saturated with the more retained species at the concentration \(c_A^*\). The choice of \(c_A^*\) is discussed in the next section. At this point it is worth noticing that the calculation of the line bb' requires the knowledge of two pieces of information. Firstly, the adsorbed amount at equilibrium \(n_A(c_A^*, 0)\), which can be measured through a frontal adsorption/desorption experiment with pure A. Secondly, the retention time \(t_B^*\) can be estimated by running before the desorption step a pulse experiment with the less retained enantiomer B.
5.2.2 Experimental procedure

The procedure presented above is now applied to the separation of the Tröger’s base enantiomers on CTA under non-linear conditions. This is particularly challenging because the separation is difficult due to the low efficiency of the stationary phase. In addition, the more retained enantiomer exhibits an unfavorable behavior at low concentrations, thus leading to significant deviation from linear adsorption equilibria. However, the adsorption behavior is favorable at high concentrations and the general assumption about the nature of the transitions (shocks and waves) is acceptable. The experimental procedure can be divided into the three following steps:

Step 1: pulse experiments

The knowledge of the Henry constants allows to calculate the complete separation region under linear conditions using Eqs (5.3) and (5.4). These are estimated through racemic pulses of decreasing volume from 5 µL to 1 µL at a total concentration of 0.2 g/L. It has been verified that for the different injected volumes, the retention times obtained are the same, thus proving that the system operates under linear conditions. The Henry constants and the void fraction used are the average values obtained over the 8 columns of the SMB unit, the maximum difference between pairs of values being 5% of the average value. These pulses on the clean columns yield $H_A = 3.5$ and $H_B = 1.9$, whereas tracer (TTBB) pulses yield $\varepsilon^* = 0.56$. The knowledge of the Henry constants is also important to design the regenerating sections. Under nonlinear conditions $m_{1,cr} = H_A$ but $m_{4,cr}$ is smaller than $H_B$, with a value depending on the feed concentration. In the experimental runs a proper safety factor must be chosen to achieve complete regeneration, as discussed in the next section. A practical approach to determine $m_{4,cr}$, without the knowledge of the whole isotherm of the less retained species, can be to start the SMB separation experiments using the smallest $m_4$ value achievable and then increasing it until the performance of the separation gets worse. It is worth noting that the only disadvantage of having $m_4$ too small is more dilution in the raffinate stream, but no hindering of the product purity.

Step 2: frontal experiment and hodograph plane analysis

The equilibrium adsorbed amounts $q_A$ and $q_B$ in Eq (5.8) are estimated by eluting the feed through a column initially saturated with the pure solvent. An on-line monitoring scheme which measures the concentration of the two enantiomers at the column outlet (see Figure 5.3) is used to calculate the area under each adsorption/desorption curve: each
experiment allows to repeat the measurement twice thus providing a double check of the amount adsorbed of each individual enantiomer.\textsuperscript{47} From these the following equilibrium loadings are estimated: $n_A = 7.2$ g/L and $n_B = 3.4$ g/L at $c^E_F = 5$ g/L, and $n_A = 14.1$ g/L and $n_B = 8.8$ g/L at $c^E_F = 16$ g/L.

The results of the two runs are better analyzed in the hodograph plane shown in Figure 5.4, i.e. the plane spanned by the concentrations of the two enantiomers. The transitions in the adsorption/desorption experiments are represented by the lines in the hodograph plane bearing the same label. The first transition, which is the breakthrough of the less retained species, is represented by a segment labeled $\Sigma_1$ along the $c_B$ axis. This transition is truncated at a point which is the intermediate state of the less retained species. The second transition $\Sigma_2$ connects the intermediate state of B to the feed point F. In the desorption experiment, the first transition $\Gamma_1$ connects the feed point F to the intermediate state of the more retained component, which is finally eluted through the last transition $\Gamma_2$. It is worth noting that the hodograph plot for the adsorption/desorption experiments does not represent the transitions in the True Counter Current equivalent to the SMB unit, since in this case the intersection of $\Sigma_1$ and $\Gamma_1$ does not correspond to the feed composition (cfr. Figure 6 by\textsuperscript{41}).

Since the objective of this procedure is to approximate the region of separation close to the optimal conditions, the pulse experiment should be run in principle at a $c^*_A$ value representative of the concentration of A achieved in section 2 under optimal conditions. This can be approximated as the concentration corresponding to the intersection of $\Gamma_1$ with the $c_A$ axis, which actually provides a reliable upper estimate of the state attained in section 2.\textsuperscript{41} In our example it is remarkable to notice that increasing the feed concentration does not change significantly the value of the intermediate state (see Figure 5.4). In the run at 5 g/L the intersection obtained by extrapolating linearly the transition $\Gamma_1$ to the axis is found to be $c_A = 1.7$ g/L, while in the run at 16 g/L the intersection is about 2.1 g/L (dashed line in Figure 5.4). This behavior, i.e. a small increase in the intermediate state for a large increase in the feed concentrations, is expected for binary competitive Langmuir systems when the concentration of the intermediate state approaches the watershed point.\textsuperscript{65} In conclusion, the value $c^*_A = 2$ g/L is chosen as representative of the optimal conditions in section 2 for both runs.

The shape of the transitions in the hodograph plane for the two runs in Figure 5.3 is different. This is the effect of the low column efficiency, which is mainly responsible for bending the transitions $\Gamma_1$ and $\Sigma_2$ in the hodograph plane for the run at high concentration (Figure 5.3b). For instance, this can be seen in Figure 5.4, where $\Gamma_1$ exhibits a spread tail.
and therefore the intermediate state is best approximated by a linear extrapolation of the transition at high concentrations. In addition, the transition $\Sigma_2$ which connects the peak of B due to the competitive adsorption of A with the feed plateau, is not monotonically decreasing as for the run at low concentration. On the contrary, at high concentrations the concentration of B along $\Sigma_2$ appears first to increase then to decrease when moving from the intermediate state to the feed state. This is surprising since a higher competition, and therefore a higher peak, is expected at high concentrations. However, the low efficiency of the stationary phase and the small difference in the breakthrough time of the transitions $\Sigma_1$ and $\Sigma_2$ prevent the development of the full peak height.

![Graph for adsorption/desorption step](image)

**Figure 5.3:** the experimental profiles for the adsorption/desorption step at the feed concentration of $c_F^A = 5$ g/l (a) and $c_F^B = 16$ g/l (b). The relative composition is 50/50.

**Step 3: frontal analysis and pulse experiment**

In order to estimate the derivative $\frac{\partial n_A}{\partial c_B} \bigg|_{(c_A^*, 0)}$ in Eq (5.9) pulse experiments with the less retained enantiomer and with $c_A^* = 2$ g/L are carried out. A 5 cm column is used in order
to reduce the amount of the more retained enantiomer needed. After loading the column at 2 g/L of the more retained enantiomer, pulses at 50 and 30 µL of pure B at 0.15 g/l are carried out. Smaller volumes were not injected because the output signal becomes comparable to the intrinsic noise. These two pulses show the same retention time, proving that the perturbation given to the system is small enough to allow a proper estimation of the derivative in Eq (5.9). The measured average retention time of the less retained enantiomer is $t_B^* = 130 \pm 3$ s. Finally, the column is desorbed and the area under the adsorption and desorption outlet concentration yields the amount of pure A adsorbed at $c_A^*$, that is $n(c_A^*, 0)$. In this experiment a value $q_A(2, 0) = 6.11$ g/L is measured. From these experiments and Eqs (5.9) and (5.10) it is possible to calculate the boundary bb' at the two concentrations of interest, as shown in Figure 5.5. It is worth noticing that the lines aa' and bb' at the two feed concentrations cross each other, as expected according to the theory. This behavior further confirms the reliability of this approach.

Figure 5.4: the adsorption/desorption experiments of Figure 5.3 in the hodograph plane. The labels refers to the transitions in Figure 5.3. The adsorption step is 40 minute long. Solid line: experimental data. Dotted line: linear extrapolation of $\Sigma_1$ to the axis $c_A$.

The approximations intrinsic to the method proposed do not have a dramatic impact on the results of Figure 5.5, since for instance the effect of axial dispersion and finite mass transfer should still be considered before analyzing the experimental performance. However, the short-cut method allows to account quantitatively for the effect of the feed concentration, which leads to a smaller region of separation. In the next section these results are used to
5.3 Effect of feed concentration on SMB behavior

Many experimental results of SMB separations run under linear conditions have been reported in the literature.\textsuperscript{16,72,76,88} However, the effect of the feed concentration on the performance of the separation has not been investigated in detail yet (cfr.\textsuperscript{7} for two experimental runs of this type). The first aim of this section is to fill this gap and to validate experimentally the behavior expected theoretically. The second aim is to show that the short-cut method is effective to design and interpret nonlinear SMB separations. The analysis of this section is carried out using the complete separation regions calculated in Figure 5.5. These regions are only an approximation of the real regions of separation, which could be calculated based on the complete knowledge of the adsorption equilibria. In addition, the experimental SMB results are affected by the low efficiency exhibited by the stationary phase and by the extracolumn dead volumes.

Six series of runs have been performed by keeping the flow rates constant and changing the switch time. The feed concentration has the values 0.2, 5 and 16 g/L of racemic mixture,
as summarized in Table 5.1. The operating points belong to a straight line almost parallel
to the diagonal as shown in Figure 5.5. In this figure the regions of separation calculated
at infinite dilution, at 5 and at 16 g/L using the short-cut approach are also drawn. Let us
notice that since the feed flow rate is constant in all the runs, the productivity of the plant
is simply proportional to the feed concentration.

The purities of the raffinate stream are controlled by the position of the operating point in
the \((\bar{m}_2, \bar{m}_3)\) plane, provided that the regeneration of the solid phase in section 1 is effective.
On the other hand, since the loop is open and the flow from section 4 is not recycled directly
to section 1, the performance of section 4 in the regenerating the mobile phase cannot affect
the purity of the extract. Nevertheless in all our experiments the stream collected at the
outlet of section 4 is always pure solvent, thus showing that the small \(\bar{m}_4\) adopted guarantees
regeneration of the mobile phase. To prove also that complete solid regeneration is attained
in section 1 one can notice that point G achieves a high raffinate purity (> 98%) using the
smallest \(\bar{m}_1\) value (Table 1). This value is 1.8 times larger than the Henry constant of the
more retained enantiomer, which is the lower bound for \(\bar{m}_1\). In the other runs always a
higher \(\bar{m}_1\) value is used and therefore complete solid regeneration is always expected. Based
on these considerations it can be concluded that in all the runs discussed here the product
purities depend only on the position of the operating point in the \((\bar{m}_2, \bar{m}_3)\) plane.

Let us first consider the runs at 0.2 g/L of feed concentration. As shown in Figure 5.6, in

Figure 5.6: purity of the extract and raffinate streams as a function of the operating parameter
\(\bar{m}_2\). Feed concentration: 0.2 g/L racemic mixture.
### Table 5.1: experimental results for the separation of Tröger's base enantiomers using an 8 column (2-2-2-2) SMB unit. The flow rates are: $Q_1=0.410$ cm$^3$/min, $Q_2=0.200$ cm$^3$/min, $Q_3=0.212$ cm$^3$/min, $Q_4=0.061$ cm$^3$/min.
Figure 5.7: purity of the extract and raffinate streams as a function of the operating parameter \( \overline{m}_2 \). Feed concentration: 5.0 g/L racemic mixture.

the series of experiments A to D the extract purities decrease from 99.3 to 94.5 %, while the raffinate purities increase from 97.4 to 98.6 %. The operating point moves from the pure extract region to the pure raffinate region achieving the best symmetric purity performance in point B, where both purities are higher than 98%. Note that according to the previous work on the Tröger’s base separation, a point is considered to belong to the separation region when both purities are above 98 %. Therefore point B in Figure 5.5 gives an indication of the position of the complete separation region at very low feed concentration. However, SMB separations on CTA can achieve higher purities. In these experiments the purities reached are limited by the purity of the feed mixture (which is > 99%) and the position of the operating points, which cannot be chosen closer to the diagonal due to the uneven distribution of the dead volumes in sections 2 and 3. In fact, when the dead volumes are unevenly distributed between sections 2 and 3 and \( V_D^3 > V_D^2 \), the region of separation in the \( (\overline{m}_2, \overline{m}_3) \) plane below the line parallel to the diagonal and corresponding to vanishing feed flow rate given by:

\[
\overline{m}_3 = \overline{m}_2 + \frac{V_D^2 - V_D^3}{V (1 - \varepsilon^*)}, \tag{5.11}
\]

cannot be accessed. In other words, the extracolumn dead volumes not only shift but also shrink the separation region.

About point A, it can be observed that a very high purity (99.3%) is obtained only in
the extract, whereas the raffinate achieves only 97.4%. Even though this point lies in the calculated ideal complete separation region in Figure 5.5, it could lie outside the actual region of separation. First of all, it must be considered that mass transfer shrinks the ideal region of separation. This effect is expected to be particularly strong under linear conditions where the self-sharpening tendency of the fronts due to nonlinear equilibria is not present. In addition, the region of separation (region 1 in Figure 5.5) is calculated under infinite dilution, while the experiment is run at a feed concentration of 0.2 g/L. The increase in the feed concentration moves the vertex downwards to the left, as shown in Figure 5.5. As a consequence, point A could be closer to the upper boundary than what Figure 5.5 shows and therefore closer to the region where only the extract is pure. This explanation suggests that point B, which is close to the lower boundary of the ideal separation region, lies inside the actual complete separation region as shown by the results of Figure 5.6.

![Figure 5.8: Purity of the extract and raffinate streams as a function of the operating parameter $m_2$. Feed concentration: 16 g/L racemic mixture.](image_url)

 Runs A, B, C and D have been repeated at a feed concentration of 5 g/L and the results are illustrated in Figure 5.7. Figures 5.6 and 5.7 exhibit a similar pattern of behavior of the extract and raffinate purities. However, two differences must be underlined. First of all, an increase in productivity leads to a worse purity performance. In fact, in the runs at 5 g/L of feed concentration the region of complete separation, i.e. where both purities are higher than 98%, is never crossed, although the rather good performance in run C indicates that this point lies close to the optimal point of the complete separation region. The second
difference is that the slope of the purity profiles in Figure 5.7 is sharper. In fact, under nonlinear conditions the region of separation becomes smaller in the neighborhood of the optimal point as shown in Figure 5.2 and the operating conditions are less robust. The corresponding region of complete separation (region 2) in Figure 5.5 shows that A and D lie in the regions of pure extract and raffinate, according to the experimental results of Figure 5.7. In particular the sharp decrease in the raffinate purity of A is the effect of the shift of the boundary \( bb' \) of the separation region due to the increase in feed concentration. Although points B and C lie inside the separation region, purities lower than 98% are attained in the raffinate and the extract, respectively. This might again be due to mass transfer limitations, which drive point B into the pure extract region and point C into the pure raffinate region.

The behavior for the runs at the feed concentration of 16 g/L is illustrated in Figure 5.8. Likewise Figure 5.7, these results show that higher feed concentrations lead to poorer performance. In fact, points C, D and E belong to the region where none of the two product streams is pure while point G is in the pure raffinate region. A comparison between Figures 5.7 and 5.8 indicates that the point achieving symmetric purities shifts toward lower \( \bar{m}_2 \) values. This behavior parallels the shift of the optimal point shown in Figure 5.5. In fact a symmetric purity in the extract and raffinate is achieved also in the region of no pure outlet above the optimal operating point. At a feed concentration of 16 g/L, higher purities could be achieved only by choosing operating points closer to the diagonal, for instance by decreasing the feed flow rate.
Chapter 6

Chromatographic reactor: enzyme catalyzed regioselective esterification

*Enzyme-catalyzed reactions are becoming increasingly important for stereoselective and regioselective transformations of fine chemicals. Although early work had focussed on aqueous-phase transformations, the relatively recent discovery that many enzymes are active in organic solvents has expanded the scope of biocatalysis to substrates and products that have little or no solubility in water. For example, in organic phases, under water-restricted conditions, synthesis rather than hydrolytic reactions are possible. Moreover, enzymes often show enhanced stability in organic media. However, control of water present in the reaction mixture is critical for these reactions. On one hand, a minimum level of hydration is required for biocatalytic activity. On the other, high water concentrations can impose thermodynamic limitations on equilibrium conversion and reduce the biocatalytic activity. Moreover, in some cases, accumulation of water can cause a permanent inactivation of the biocatalyst if a free water phase is allowed to form in the reactor.

The problem of water control is exacerbated in reactions where water is a product, such as esterifications. In this case, the design of optimum continuous-flow reactors must take into account the evolution of water in the system and its partitioning between biocatalyst and reaction mixture. Adsorptive methods are particularly well suited for the control of water in these reactions as adsorbents can be easily integrated for operation in packed-bed reactors together with an immobilized biocatalyst. Mensah et al., for example, have shown that catalytically inert ion-exchange resins are effective as water adsorbents for in situ control of water in irreversible enzymatic esterifications. In this case, the reactor can be operated in a cyclic manner, being alternately supplied with the substrate feed and

*In collaboration with Jonathan P. Meissner, University of Virginia
with a regenerant stream to periodically remove water accumulated on the biocatalyst and on the adsorbent. Regeneration can be accomplished by desorption with a polar solvent. Thus, this can be done without separating the adsorbent from the biocatalyst. In principle, other adsorbents, such as zeolites, can be used. However, such adsorbents tend to strip the essential water from the enzyme\textsuperscript{101} and cannot be regenerated without separating them from the biocatalyst, since very high temperatures are required.

The adsorption-assisted operation of enzymatic esterifications can provide two distinct advantages. On one hand, simultaneous adsorption reduces accumulation of water on the biocatalyst maintaining high activity and preventing irreversible inactivation. On the other, continuous removal of water can improve productivity by shifting the thermodynamic reaction equilibrium toward high conversions during the transient operation of the reactor. Adsorptive or chromatographic reactors where reaction and separation of products take place simultaneously have been proposed for different reactions in the petrochemical industry, such as hydrogenations\textsuperscript{22} and oxidative methane coupling,\textsuperscript{20} and in fine chemistry, such as sulfonic acid resin-catalyzed esterifications, transesterifications, etherifications and acetylations.\textsuperscript{23,35,58,102} Adsorption-enhanced enzymatic esterifications have also been considered for the case of an essentially irreversible reaction by Mensah et al.\textsuperscript{97,100,103} The reaction considered was the esterification of propionic acid and isoamyl alcohol in a hexane solvent. In this case, because of the presence of an excess solvent, nearly complete conversion is attainable even without water removal. However, productivity is limited by the decrease in enzyme activity caused by accumulation of water on the biocatalyst. Cyclic operation in an adsorptive reactor was shown to yield much greater productivity.

In this chapter, an equilibrium-limited enzymatic esterification is studied. In this case, additional productivity improvements are possible as a result of the reduction in equilibrium limitations. As a model, we consider the selective esterification of propionic acid and 2-ethyl-1,3-hexandiol using an immobilized lipase preparation as the biocatalyst. Only the monoester is formed because of the specificity of the enzyme for primary alcohols. However, due to the polarity of the monoester product, the solubility of water in the system remains high during the course of the reaction. As a result, the conversion is equilibrium limited. This behavior is different from other esterifications where the conversion of the alcohol to a nonpolar ester dramatically reduces the water solubility, allowing complete conversion. Experimental results obtained in batch and fixed bed reactors are discussed and explained through a quantitative model. The effects of \textit{in situ} adsorptive water removal on reaction rate and conversion are studied and guidelines for process optimization and scale-up are discussed in light of a model taking into account the interplay of adsorptive and reactive phenomena.
6.1 Reaction kinetics

In the presence of Lipozyme, propionic acid and 2-ethyl-1,3-hexanediol in hexane are converted to the primary monoester and water. The reaction is highly regiospecific and formation of the diester was not detected even after 50 hours of reaction time. Since neither the ester nor the diol are significantly adsorbed by Lipozyme, it is possible to determine initial reaction rates in a stirred vessel from the slope of their respective concentration profiles. The initial concentrations and three concentration measurements during the first hour of operation were found to be linearly correlated (with correlation coefficient greater than 0.99). Hence, these data were used to calculate initial rates for different initial acid and diol concentrations. The values obtained with the ester or diol profiles were nearly coincident.

![Graph](image)

Figure 6.1: initial reaction rate data for Lipozyme-catalyzed esterification of propionic acid and 2-ethyl-1,3-hexanediol in hexane. Lines are calculated from Eq. (6.1) with the parameters of Table 6.1.

Experimental results are shown in Figure 6.1. The initial rate increases with diol concentration, but decreases with acid concentration, suggesting substrate inhibition. A similar behavior was observed for the reaction of propionic acid with isoamyl alcohol on Lipozyme.\textsuperscript{100} However, a strong inhibitory effect of polar alcohols with a shorter chain, such as ethanol, has also been reported for Lipozyme.\textsuperscript{93} In our case, we found that inhibition by the diol was very small. It should be noted that Lipozyme remains stable even in concentrated solutions of the diol in hexane (up to at least 3 mol/L) and is stable in pure isoamyl alcohol. However, it becomes irreversibly inactivated in hexane solutions containing more than 2 mol/L acid.

The rate data of Figure 6.1 can be described in terms of the classical "ping-pong bi-bi"
Table 6.1: fitted constants in reaction kinetic model. Initial reaction rate for the fresh catalyst ($n_w^c = 2.4$ mmol/g).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>$r_m^0$</td>
<td>2.6</td>
<td>mmol/(h g)</td>
</tr>
<tr>
<td>$K_{d,diol}^m$</td>
<td>$6.5 \cdot 10^{-5}$</td>
<td>mol/L</td>
</tr>
<tr>
<td>$K_{acid}^m$</td>
<td>$3.0 \cdot 10^{-2}$</td>
<td>mol/L</td>
</tr>
<tr>
<td>$K_{diol}^i$</td>
<td>5.0</td>
<td>mol/L</td>
</tr>
<tr>
<td>$K_{acid}^i$</td>
<td>$11 \cdot 10^{-5}$</td>
<td>mol/L</td>
</tr>
</tbody>
</table>

The initial reaction rate for the fresh catalyst is given by:

$$r = \frac{r_m c_{acid} c_{diol}}{c_{acid}c_{diol} + c_{acid} K_{d,diol}^m \left(1 + \frac{c_{diol}}{K_{diol}^i}\right) + c_{diol} K_{acid}^m \left(1 + \frac{c_{acid}}{K_{acid}^i}\right)}$$

(6.1)

where $r_m$ is the forward rate constant, $K_{d,diol}^m$ and $K_{acid}^m$ are Michaelis-Menten constants for the diol and acid substrates, and $K_{diol}^i$ and $K_{acid}^i$ are dissociation constants for the formation of dead-end complexes with the biocatalyst. The values of these parameters were determined by non linear least square fitting of the data and are reported in Table 6.1. The agreement between the model fit and the experimental data, shown in Figure 6.1, is within experimental error. As expected from the experimental behavior, the diol inhibition constant, $K_{diol}^i$, is orders of magnitude larger than the one for the acid, $K_{acid}^i$, consistent with the fact that diol inhibition plays only a small role.

It should be noted that the rate data in Figure 6.1 pertain to the fresh catalyst with a water content of 2.4 mmol/g. As shown by Mensah et al.\textsuperscript{100} for the reaction of propionic acid and isoamyl alcohol on Lipozyme, varying the water content of the biocatalyst affects the reaction rate. However, the dependence of the kinetic behavior on substrate concentration remains the same. Thus, the effect of water content can be described by introducing an empirical functional dependence of the rate constant $r_m$ on the water content of the biocatalyst in the form:

$$r_m = r_m^0 \cdot f\left(n_w^c\right),$$

(6.2)

where $r_m^0$ is the rate constant for the fresh catalyst and $f\left(n_w^c\right)$ is the rate relative to that obtained with the fresh catalyst at the same concentrations of acid and diol substrates.

Figure 6.2 shows the initial rate for the diol reaction on Lipozyme relative to the fresh catalyst at different water contents with the same acid and diol concentrations. Literature results show that at increasing water loading the initial reaction rate can either decrease\textsuperscript{100,104} or
be bell-shaped. In our case the reaction rate always decreased, but the smallest water content investigated was 1.4 mmol/g. Since water removal from the biocatalyst by the reactor regeneration method discussed in the next section did not allow reaching lower water contents, the range studied is adequate for our purposes. Thus, following the approach of Mensah et al., we represented the data with the empirical function:

$$f(n_w^c) = 0.63 - 0.35 \tanh \left( \frac{n_w^c - 5}{1.5} \right). \quad (6.3)$$

As seen in Figure 6.2, there is a sharp decrease in catalytic activity at water contents between 4 and 6 mmol/g, where almost 60% of the activity of the enzyme is lost. Therefore, control of water accumulation on the biocatalyst is important to optimize batch and fixed bed reactors. The esterification of isoamyl alcohol also showed a pronounced rate decrease with water content, but this occurred more gradually over the range 0-12 mmol/g. For the diol reaction, the biocatalyst can work in two regimes corresponding to high and low reaction rates separated by a sharp transition.

Application of the kinetic model to the prediction of reactor behavior for finite conversion levels also requires an understanding of the backward reaction and of product inhibition. Batch runs (see Figures 6.4 and 6.5) show that at equilibrium the amount of water in the liquid phase is not negligible. Thus, several long-term batch reaction runs (50 hour) starting with different initial concentrations in the range 0.1 - 1 mol/L were used to determine an apparent equilibrium constant $K_{eq}$ based on substrate and product concentrations. The resulting $K_{eq}$ varied over the small range 0.6 ±0.1. It must be emphasized that this result is
peculiar for our system, since, in general, the calculation of the equilibrium constant should be carried out using activities instead of concentrations.\textsuperscript{105,106} Thus, for other systems, where the polarity of the ester product is very different, the apparent equilibrium constant can change over a much larger range.

The results of the batch runs in Figures 6.4 and 6.5 show that the reaction is close to equilibrium after 24 hours. Thus a quantitative description of the backward reaction is needed. According to the "ping pong bi-bi model" an exact formulation would require the determination of a large number of parameters. However, a simple semiempirical model can be obtained with the following expression:

\[
 r = \frac{r_m \left( c_{\text{acid}} c_{\text{dil}} \frac{c_{\text{ester}} c_{\text{water}}}{K_{\text{eq}}} \right)}{c_{\text{acid}} c_{\text{dil}} + c_{\text{acid}} K_{\text{dil}} + c_{\text{dil}} K_{\text{acid}} \left( 1 + \frac{c_{\text{acid}}}{K_{\text{acid}}} + c_{\text{dil}} K_{\text{dil}} \left( 1 + \frac{c_{\text{dil}}}{K_{\text{dil}}} \right) \right) (6.4)}
\]

In this description, we neglect inhibition and binding of the ester to the biocatalyst, since these effects were shown to be unimportant for isoamyl propionate\textsuperscript{100} and are likely insignificant for the diol monoester. The inhibitory effect of water is retained through the dependence of the rate constant \( r_m \) on the water content of the biocatalyst given by Eq. (6.3). Finally, thermodynamic equilibrium is described through the apparent equilibrium constant \( K_{\text{eq}} \). This is assumed to have the constant value of 0.6. Although this expression is only approximate, as will be shown later, it provides an excellent description of batch and fixed bed reactor behavior, justifying the validity of this semiempirical approach. It is worth noticing that, when either the acid or the diol is absent and both products are present, the reaction rate given by Eq. (6.4) would be infinite. In practice this never happens in the batch and fixed bed runs reported in this paper and therefore Eq. (6.4) remains meaningful over the whole range of conditions of interest here.

A final consideration regards the possible role of mass transfer limitations on the determination of reactions rates. The value of the reaction rate constant \( r_m^0 \) is similar to the one previously reported for the esterification of isoamyl alcohol with propionic acid.\textsuperscript{100} Using the proposed kinetic model it is possible to calculate the effectiveness factor of the catalyst. Previous results based on the calculation of the generalized Thiele modulus for the esterification of isoamyl alcohol and propionic acid yielded an effectiveness factor close to one.\textsuperscript{100} Similarly, we conclude that the mass transfer limitations do not play an important role in the determination of the kinetic parameters for this system since the reaction rate and the substrates do not differ significantly. However, in general, intraparticle mass transfer can control reactions catalyzed by immobilized enzymes and its importance has to be assessed on a case by case basis.\textsuperscript{95}
6.2 Adsorption equilibria

Adsorption equilibrium isotherms for water on Lipozyme and on the Dowex resin are shown in Figure 6.3. The adsorption data for water from diol-hexane solutions are displayed as a function of the thermodynamic activity of water. The latter was calculated from the UNIFAC model as discussed by Mensah et al. Data obtained by Mensah et al. for the adsorption of water from hexane solutions containing propionic acid, isoamyl alcohol, and isoamyl propionate in different concentrations and for the adsorption of water from isoamyl alcohol are also included. It is evident that, when plotted in terms of thermodynamic activity, the isotherms for each material collapse onto single curves. Thus, these isotherms allow a calculation of the amount of water adsorbed at equilibrium as a function of the varying concentrations of substrates and products at different times in a batch reactor or along the length of a fixed-bed reactor. The following empirical expressions were used to fit the adsorption isotherm data over the range $0 < a_w < 0.8$:

For Lipozyme:

$$n_w^c = 13.6a_w - 19.7a_w^2 + 22.2a_w^3$$  \hspace{1cm} (6.5)

For Dowex HCR-W2/Na form:

$$n_w^a = 54.6a_w - 106a_w^2 + 105a_w^3$$  \hspace{1cm} (6.6)

where $n_w^c$ and $n_w^a$ are in mmol/g. The water adsorption affinity is much higher for the Dowex resin than for Lipozyme. This occurs because these polymer-based materials adsorb water by hydration of ionogenic groups. Hence, when the two materials are present simultaneously, water is preferentially adsorbed on the Dowex resin that contains a high concentration of sulfonate groups. On the other hand, both isotherms are fairly linear and become unfavorable at high $a_w$-values, indicating that regeneration by desorption at constant temperature is possible.

Although the Dowex resin is highly selective for water, Lipozyme also adsorbs propionic acid. Adsorption of the acid, which is strongly non-linear and shows a very favorable isotherm, can also be expressed as a function of its thermodynamic activity. Mensah et al. provide the expression:

$$n_w^c = \frac{57.2a_{acid}}{1 + 19.7a_{acid}}.$$  \hspace{1cm} (6.7)

where $n_w^c$ is in mmol/g. The uptake of propionic acid is not significantly affected by the water content of the biocatalyst, thus the adsorption can be considered non-competitive.
6. Chromatographic reactor: enzyme catalyzed regioselective esterification

6.3 Batch reactor behavior

The concentration profiles for the batch esterification of a 1 mol/L solution of propionic acid and 2-ethyl-1,3-hexanediol in hexane on Lipozyme are shown in Figure 6.4. The acid adsorbs on the biocatalyst and therefore a sharp drop in its concentration occurs for very short times. As the reaction proceeds, the acid and the diol concentrations decrease at the same rate and their profiles remain parallel. The concentrations of the monoester and water products increase as the reaction proceeds, leveling off after about 24 hour of reaction time. Clearly, much less water is present in solution as compared to monoester. This occurs as a result of water adsorption on the biocatalyst. At equilibrium, nearly half of the water formed remains adsorbed on the biocatalyst for these reaction conditions. This behavior is different from that observed for the reaction of propionic acid and isoamyl alcohol. In that case, the ester product is non-polar. As a result, the solubility of water in the reaction mixture becomes extremely low as the reaction proceeds. Thus, the water concentration in solution initially increases and then decreases. At equilibrium, nearly complete conversion is obtained with essentially all the water in an adsorbed state.
The effect of adding Dowex in the sodium form is illustrated in Figure 6.5. Although the results show a trend similar to that in Figure 4, much more water is adsorbed away from the reaction mixture and a much higher conversion level is attained at equilibrium. Two mechanisms increase the reaction rate with respect to the previous run. Firstly, accumulation of water on the enzyme is reduced and, therefore, according to the data in Figure 6.2, the catalytic activity is higher. Secondly less water is available in the reaction mixture for the backward reaction. As a result the equilibrium conversion is achieved much sooner than in Figure 6.4. Note that in the absence of adsorption, an increase in conversion would require a longer process time. However, addition of the Dowex resin provides a higher conversion over a similar reaction time, thus effectively improving the reaction rate during the whole run. The decreased water availability in the liquid phase obviously leads to different fluid
phase concentrations at equilibrium.

![Graphs](image)

Figure 6.5: experimental and predicted behavior of batch esterification of 2-ethyl-1,3-hexanediol and propionic acid in hexane with Dowex HCR-W2/Na-form as water adsorbent. Initial substrate concentration 1 mol/L. Lipozyme weight=0.1 g, Dowex weight=0.15 g, solution volume= 2 cm$^3$.

(a) experimental and predicted concentration profiles, (b) predicted water activity and activity coefficient, (c) predicted water content of Lipozyme and Dowex resin.

The behavior of the batch reactor can be predicted quantitatively using a model accounting for the interplay of reaction kinetics and selective sorption on the biocatalyst and the Dowex resin. The model used here has been proposed by Mensah et al.$^{100}$ and is briefly summarized in the following. Adsorption of water and acid on Lipozyme is assumed to be non-competitive; only water is assumed to be adsorbed onto the Dowex resin; the amount of water adsorbed both on the Dowex and on the biocatalyst from solutions of different compositions depends only on the thermodynamic activity of water; the water activity coefficients are estimated based on the UNIFAC model taking into account the mole fractions of all the five components.$^{58,100,107}$
The behavior of the batch reactor is described by the following system of ordinary differential equations written for each species:

\[ V \frac{dc_i}{dt} + m_c \frac{dn_i^c}{dt} + m_a \frac{dn_i^a}{dt} = m_c \nu_i r (c, n_{w_i}) \]  
(6.8)

\[ \frac{dn_i^c}{dt} = k_i^c (n_{i^c,eq} - n_{i^c}) \]  
(6.9)

\[ \frac{dn_i^a}{dt} = k_i^a (n_{i^a,eq} - n_{i^a}) \]  
(6.10)

In these equations \( V \) is the solution volume, \( m_c \) and \( m_a \) are the masses of biocatalyst and adsorbent respectively, and \( r \) is the reaction rate. The latter is given by Eqs. 6.2, and 6.3. Although the effectiveness factor of the biocatalyst is essentially 1, adsorption of water and acid can still occur at finite rates. Equations (9) and (10) are thus used to represent these rates through a solid film linear driving force model. The mass transfer rate is assumed to be proportional to the difference between the composition of the adsorbed phase at equilibrium with the local fluid phase \( (q_{i^c,eq}) \) and the actual adsorbed phase composition \( (n_i) \). The mass transfer parameters \( k_i^c \) and \( k_i^a \) describe the rate of adsorption on the catalyst and on the adsorbent, respectively. Evaluation of these parameters is discussed in next section.

However, it should be noted that the behavior of the batch reactor is largely unaffected by their values since, for these conditions, the characteristic times for reaction are much larger than the characteristic time for adsorption.

Model predictions of the batch reactor behavior based on the independently derived parameter values are shown in Figures 6.4 and 6.5. In addition to the concentration profiles, the predicted thermodynamic activity and activity coefficient of water, and the adsorbed water concentrations are also shown. Experimental and predicted concentration profiles are in good agreement in both cases. For the case of Lipozyme alone, as seen in Figure 6.4b, the activity coefficient of water remains fairly constant during the course of the reaction. However, the water activity increases substantially approaching values around 0.75 at the end of the run. Consequently water loading on the biocatalyst approaches 8 mmol/g (see Figure 3). For these conditions, as shown in Figure 6.2, the activity of the biocatalyst is only about 30% of the activity of the fresh material. As seen in Figure 6.4c predicted and experimental water loadings on the biocatalyst are in excellent agreement.

As seen in Figure 6.5b, addition of the Dowex resin reduces the thermodynamic activity of water in solution. In this case, most of the water formed in the reaction is adsorbed by the resin and the predicted water loading on the biocatalyst remains well below 3 mmol/g. For these conditions, the activity of the biocatalyst remains close to one and a much faster conversion of the substrates is observed. The equilibrium conversion is also improved, of course, since the water concentration in solution is kept very low. We did not determine
experimentally the amount of water adsorbed individually by Lipozyme and by the Dowex resin. However, the total amount of water adsorbed is consistent with the predicted value as implied by the good agreement between experimental and predicted water concentration profiles.

**Figure 6.6**: experimental and predicted effluent profiles for Lipozyme catalyzed esterification of 2-ethyl-1,3-hexanediol and propionic acid in hexane in a fixed bed reactor containing Lipozyme alone. Feed: propionic acid 1 mol/L, diol 1.05 mol/L. Lipozyme weight = 4.0 g, bed length = 5.4 cm, flow rate = 0.21 cm³/min. Initial condition: water on Lipozyme 1 mmol/g. (a) reaction run, (b) predicted water and propionic acid activity, (c) predicted water content of Lipozyme. Broken line: t = 0.5 h. Dotted line: t = 1.5 h. Solid line: steady state.

### 6.4 Fixed bed reactor behavior

Representative concentration profiles for a fixed-bed reactor run with a 1 mol/L equimolar feed mixture of the reactants are shown Figure 6.6a. In this case, the reactor was packed...
with 4 g of Lipozyme and initially equilibrated with hexane. The dynamic behavior is complicated by the simultaneous occurrence of adsorption. A transient period is followed by a gradual approach to steady-state conditions. As the reactants enter the column they are converted to the diol monoester and water. Propionic acid and water are adsorbed on the catalyst while diol and ester move ahead of the reaction front. The breakthrough time of ester and unreacted diol is equal to the residence time of a non-retained tracer. Initially, the reaction occurs only near the reactor entrance. However, as the propionic acid front moves down the reactor, reaction takes place over a greater length of the bed. Thus, during the initial transient period, the diol concentration decreases while the ester concentration increases. The reactive front of propionic acid and water breaks through at the same time as the maximum in the ester profile.

In the case of no reaction, and with a feed consisting of water and propionic acid, breakthrough of water would occur much later after the acid breakthrough due to the larger water uptake capacity of Lipozyme. However, under reactive conditions, water is produced at the reaction front. Thus, the reaction couples the adsorptive fronts of water and acid together. This behavior is typical of adsorptive or chromatographic reactors and has already been observed for non-enzymatic reactions. The breakthrough profiles of water and propionic acid are sluggish and the achievement of steady state conditions requires a long time. When the reactive front breaks through, the ester concentration declines while the the diol concentration increases to the steady state value. For this run, the steady-state conversion is 78 % of the equilibrium conversion. The difference in the area between the ester and the water profile is proportional to the amount of water adsorbed on the biocatalyst. As a result of the selective adsorption of water, a substantial improvement in conversion is seen during the transient phase. As the water adsorption capacity of the biocatalyst is gradually consumed, however, this improvement over the steady-steady value vanishes as the effluent attains the final concentrations.

At the end of the run the column was flushed with a few bed volumes of hexane. The reactor was then regenerated by feeding a diol/hexane 70/30 (v/v) mixture to remove the adsorbed species. Regeneration was achieved in 4 hours at the flow rate of 0.47 cm³/min. After flushing 2 bed volumes of hexane, the reactor was ready for another reaction step. The run in Figure 6.6 to 6.10 were then repeated after regeneration and essentially identical results were obtained. This proves that the enzyme regained its original activity when the initial low level of hydration was restored.

Since conversion can be improved during transient operation, it is desirable to predict the dynamic behavior of the reactor. Optimum conditions are dependent on the establishment
of an adequate water activity profile along the reactor. Thus, a model taking into account the spatial variations in substrate and product concentrations is needed. The following equations and boundary conditions can be used to describe the transient behavior:

\[
\frac{\varepsilon}{\partial t} c_i + \rho c \frac{\partial n_i^c}{\partial t} + \rho_a \frac{\partial n_i^a}{\partial t} + u \frac{\partial c_i}{\partial z} = \varepsilon_d D_L \frac{\partial^2 c_i}{\partial z^2} + \rho c \mu r (c, n_i^w) \quad (6.11)
\]

\[
\frac{\partial n_i^c}{\partial t} = k_i^c (n_i^{c,eq} - n_i^c) \quad (6.12)
\]

\[
\frac{\partial n_i^a}{\partial t} = k_i^a (n_i^{a,eq} - n_i^a) \quad (6.13)
\]

\[
z = 0 : \quad u c_i = u c_i - \varepsilon_d D_L \frac{\partial c_i}{\partial z} \quad (6.14)
\]

\[
z = L : \quad \frac{\partial c_i}{\partial z} = 0 \quad (6.15)
\]

where \(\varepsilon\) is the bed void fraction, \(\rho c\) and \(\rho_a\) are the catalyst and adsorbent weights per unit bed volume, \(u\) is superficial velocity and \(D_L\) is the axial dispersion coefficient. These equations are written for each of the five species present in the reactor system (acid, diol, ester, water, and hexane) and coupled with the rate and equilibrium expressions previously described. The resulting equations are solved with the method of lines using an upwind finite difference scheme.

The model parameter values were determined as follows. The axial dispersion coefficient \(D_L\) was determined by tracer experiments.\(^{97}\) A value of \(Pe = 0.3\), in good agreement with the empirical correlation of Chung and Wen,\(^{108}\) was found. For columns packed with both Lipozyme and the Dowex resin, the column porosity was calculated from:

\[
\varepsilon = \varepsilon_b + (1 - \varepsilon_b) \varepsilon P \phi_c \quad (6.16)
\]

where \(\phi_c\) is the volume fraction of Lipozyme in the packed bed and \(\varepsilon_b = 0.4\). Finally, the mass transfer parameters for the adsorption of the acid on Lipozyme and for the adsorption of water on Lipozyme and the Dowex resin were also previously reported as: \(k_{\text{acid}}^c = 1.3 \text{ h}^{-1}\), \(k_{\text{water}}^c = 7.9 \text{ h}^{-1}\) and \(k_{\text{water}}^a = 1.3 \text{ h}^{-1}\). These parameters were estimated from single-component column breakthrough experiments.\(^{97}\) The same parameter values could be used for our system. However, in order to obtain a somewhat better match of the acid breakthrough curves under reactive conditions, we found it was necessary to use a higher value of \(k_{\text{acid}}^c = 3 \text{ h}^{-1}\). It should be noted that the estimation of the mass transfer coefficient of the acid from breakthrough experiments is difficult because of the very favorable nature of the acid adsorption isotherm. Thus, the value used in this work is not inconsistent with the single-component breakthrough behavior. The remaining parameters, kinetics and isotherm expressions were employed without adjustment. The UNIFAC model was used at
each numerical integration step to estimate the thermodynamic activities along the reactor length.

Predicted effluent profiles, shown in Figure 6.6a, are in excellent agreement with the experimental ones. In particular, the model accurately predicts the breakthrough of the acid and water fronts. Predicted thermodynamic activity and adsorbed-water concentration profiles along the reactor at different times during the transient and at steady state are shown in Figure 6.6b and 6.6c. The steady-state profiles are calculated directly from the solution of the following equation:

$$\frac{d c_i}{dx} = \frac{\varepsilon_b D_L c_i}{u L} \frac{d^2 c_i}{dx^2} + \frac{m_c}{Q} \nu_i r (c, n_w^c),$$

where $x = z/L$ is the dimensionless reactor length. The flow rate $Q$ and the mass of catalyst in the reactor $m_c$, are 0.21 cm$^3$/min and 4 g, respectively, in all runs. The only term that depends on reactor length is that associated with axial dispersion; the results of the numerical simulations show, however, that the contribution of this term is small for our system and can be neglected with little error. As a consequence, the internal profiles as a function of $x$ and, hence, the conversion for runs at the same feed concentration are essentially coincident whatever the amount of Dowex added.

Significant insight can be obtained by inspecting the internal profiles. Firstly, the water activity profiles at different times, shown in Figure 6.6b, confirm that in this run a water bulk phase is not formed. As previously discussed, the polarity of the monoester produced prevents the water saturation of the organic phase. In turn, this prevents irreversible deactivation of the enzyme and allows a stable steady-state operation of the reactor. The maximum in the ester profile can be explained by inspection of the internal concentration and local reaction rate profiles, which are shown in Figure 6.7. At early times (see broken lines in Figure 6.7) the reaction rate $r$ remains nearly constant along the reactor length up to the point where the propionic acid concentration goes to zero. For short times, the effect of water accumulation is negligible and $f (n_w^c)$ is close to 1. The highest instantaneous conversion is obtained when the reactive acid front breaks through (dotted line). After breakthrough of the acid, the conversion gradually decreases as water accumulation on the biocatalyst along the reactor length (see Figure 6.6c) causes a low reaction rate in the major part of the reactor (Figure 6.7). Finally, we can see that at steady state the fixed bed reactor can be viewed as divided in two parts, about equal in length. In the part closest to the entrance accumulation of water is low and does not greatly affect the activity of the biocatalyst (as was the case for the batch reactor at small conversions). Conversely, in the part closest to the exit accumulation of water on the biocatalyst is substantial (above 4 mmol/g) and reduces the activity (as was the case for the batch reactor with only Lipozyme
Figure 6.7: experimental and predicted effluent profiles for Lipozyme catalyzed esterification of 2-ethyl-1,3-hexanediol and propionic acid in hexane in a fixed bed reactor containing Lipozyme alone. Feed: propionic acid 1 mol/L, diol 1.05 mol/L. Lipozyme weight=4.0 g, bed length=5.4 cm, flow rate=0.21 cm³/min. Initial condition: water on Lipozyme 1 mmol/g. (a) reaction run, (b) predicted water and propionic acid activity, (c) predicted water content of Lipozyme. Broken line: t=0.5 h. Dotted line: t=1.5 h. Solid line: steady state.

at high conversions).

The effects of feed concentration and the addition of Dowex resin as a water adsorbent were studied experimentally and by simulation. Figure 6.8 shows experimental and predicted profiles for an equimolar feed of 0.5 mol/L propionic acid and diol in hexane. The effluent profiles in Figure 6.8a are qualitatively the same as those in Figure 6.6. The diol exhibits first a maximum and then a minimum and the ester concentration has a maximum when the reactive front breaks through. However, there are two important quantitative differences. First, the breakthrough time of the reactive front is substantially delayed. Second, the predicted thermodynamic activity of water at steady state is predicted to exceed 1. In practice this cannot occur, but, as shown by Mensah et al.,97 is an indication that if this run were continued for longer times, a bulk water phase would be formed leading to irreversible deactivation of the enzyme. The acid sorption capacity of the Lipozyme is a function of the acid activity according to Eq. (6.7). A comparison between the activity profiles in Figures 6.6b and 6.8b shows that when feeding a dilute solution the activity of water increases while the activity of the acid decreases only slightly with respect to the more concentrated case. Therefore the breakthrough of the acid is delayed since the same acid adsorptive capacity is available while the amount of acid fed is smaller.
The effects of adding Dowex resin to control accumulation of water on the biocatalyst is shown in Figure 6.9. This figure shows experimental and predicted profiles for an equimolar feed containing 1 mol/L in hexane in a reactor packed with 4 g of Lipozyme and 4 g of the Dowex resin. The pattern of behavior discussed above for the runs in Figures 6.6 and 6.8 is still seen even though the profiles are quantitatively different. The length of the column $L$, the catalyst density $\rho_c$ and the overall porosity $\varepsilon$ change upon packing with Lipozyme and Dowex. However, the steady state profiles in Figures 6.6 and 6.9 are identical when plotted against the dimensionless axial coordinate $x$, since the same amount of catalyst has been used. In this run a proportionately longer part of the reactor is available for conversion of the reactants and, therefore, even if the catalyst density is lower, the same steady state conversion is achieved as in the run at high feed concentration without Dowex. However the transient behavior of the reactor is different. First of all, the largest instantaneous conversion in Figure 6.9 is enhanced with respect to Figure 6.6. The enhancement of conversion (64%
Figure 6.9: experimental and predicted effluent profiles for Lipozyme catalyzed esterification of 2-ethyl-1,3-hexanediol and propionic acid in hexane in a fixed reactor containing Lipozyme and Dowex HCR-W2/Na form. Feed: propionic acid 1.05 mol/L, diol 1.05 mol/L, water 0.02 mol/L. Lipozyme weight=4.0 g, Dowex resin weight=4.0 g, bed length=7.9 cm, flow rate=0.21 cm³/min. Initial condition: water on Lipozyme 2 mmol/g, water on Dowex resin 5 mmol/g. (a) reaction run, (b) predicted water content of Lipozyme and Dowex. Broken line: t=0.5 h. Dotted line: t=1.5 h. Solid line: steady state.

compared to 44%) during the transient period is due to the separation of water from the reaction mixture. As shown in Figure 6.9b until the reactive front breaks through, the amount of water onto Lipozyme is predicted to remain well below 4 mmol/g. Thus the biocatalyst activity remains close to the initial value. Moreover, the time to achieve steady state is about 20 hours, because of the large water uptake capacity of the Dowex resin. Thus, a longer period where conversion is enhanced relative to the steady-state value is obtained.

Next, we consider the case of a reaction conducted with a low feed concentration (0.5 mol/L) in a reactor packed with Lipozyme and Dowex resin. The dynamic behavior shown in Figure 6.10 can be understood using the same arguments discussed before. The same steady state profiles as in Figure 6.8 are obtained. Thus, as in the previous case, formation of a water bulk phase might prevent a stable continuous operation of the reactor. We have explained
before (Figure 6.8b) that one of the effects of a smaller feed concentration is to delay the breakthrough of the reactive front. In addition, in Figure 6.9 it is shown that the removal of water by Dowex prevents high water activities during the transient and reduces water accumulation on the Lipozyme leading to a maximal instantaneous conversion (80%) which is the largest obtained.

Finally, we analyze and compare the behaviors observed in the different runs during the transient period, i.e. before breakthrough of the reactive front. Among the runs reported the best ester productivity per mass of Lipozyme is achieved by the run at low feed concentration using the column packed with Lipozyme and Dowex. Two mechanisms are responsible for this result. In fact, both the delay in the acid breakthrough (due to the dilute feed solution) and the reduced accumulation of water on Lipozyme (due to the Dowex resin), enhance the performance of the reactor during the transient period. Conversion during the transient period is improved by lowering the feed concentration, since not only the feed concentration controls the performance directly by increasing the throughput but also indirectly by changing the dynamics of the reactor.
6. Chromatographic reactor: enzyme catalyzed regioselective esterification
Chapter 7

Chromatographic reactor: esterification catalyzed by ion-exchange resins

*The aim of this chapter is to study the performance of the chromatographic reactor with respect to reactions catalyzed by ion-exchange resins, such as esterifications, transesterifications and acetilations. The model presented in this chapter is needed for the scale up of the process to the SMB scale, which will be discussed in the next chapter.

Although the subject of this and of the previous chapter is similar, the approach adopted is very different. In the case of enzyme catalyzed reaction the feed mixture is diluted in an inert solvent, since the enzyme might be denatured at high concentrations of reactants. In the case of ion-exchange resins the feed mixture is not diluted and one of the reactants is used as solvent. In the following it is discussed how these differences affect both the adsorption behavior and the dynamics of the reactor. Moreover, the catalytic activity of the enzyme is not constant and the effect of the accumulation of the products on the support has to be taken into account to model the system. This is not true for ion-exchange resins where the accumulation of the products on the resin does not affect the rate constants. From this perspective, the two model systems might be considered as representative models for a large class of applications. In fact, the comparison of the two chapters highlights the different model strategies and the different reactor behaviors for systems with or without solvent.

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7. Chromatographie reactor: esterification catalyzed by ion-exchange resins

7.1 Thermodynamics

Polymer resins in contact with pure solvents exhibit swelling. This is due to the solvent uptake in the polymer matrix driven by the activity gradient. The extent of polymer swelling is controlled both by the structure of the material (cross-links, functional groups) and properties of the solvent, such as pH, among others system variables such as temperature. The polymer swelling has been the subject of extensive investigations. In fact, the design of polymeric materials with well-defined swelling properties has promising applications in controlled drug delivery,\textsuperscript{109} in the design of biosensors and environmentally sensitive membranes.

Polymeric resins in contact with a mixture exhibit not only swelling but also selective sorption and therefore they are suitable stationary phases in chromatography. The most widespread application of resins as stationary phases is the selective removal of organic compounds from water or vice versa of water from organic mixtures. However, applications so diverse as selective purifications needed in high throughput screening are carried out nowadays using resins designed for the specific purpose.

Finally, functionalized polymeric materials are heterogeneous catalysts for a broad class of reactions. In some applications the functional groups that are responsible for the selective uptake of the resin are also catalytically active.\textsuperscript{23,58} For example, acidic ion-exchange resins can be used to uptake selectively water from organic mixtures by hydration of the ionogenic groups.\textsuperscript{110} In addition, the same groups can be exploited to catalyze reactions such as esterifications and acetylations. However, in other cases the catalytic sites may be distinguishable. For instance, catalytically active enzymes supported on matrixes uptaking water are commercially available.\textsuperscript{100}

Swelling is of no interest in reactive chromatography and will not be considered in the following. In fact, the need of a stable packing exhibiting good mechanical properties calls for a strict control of swelling. A distinction must be made between two kind of systems, depending on the use of a solvent. Systems where no solvent is used and large composition changes occur may exhibit substantial swelling which can be controlled using highly cross-linked materials, such as the Amberlyst 15 used in this work. On the other hand, diluted systems show a negligible swelling due to composition changes. The difference between these two kinds of systems does not only involve the swelling behavior but also the the description of adsorption equilibria. In fact, equilibria in diluted systems can be accurately described with empirical models\textsuperscript{100,111} while the absence of a solvent limits the applicability of this simple approach.

The aim of this section is to describe multicomponent equilibria for the system of interest
in order to describe the catalytic activity of the resin and the dynamic behavior of the chromatographic reactor discussed in the next sections. In the description of the multicomponent equilibria in a reactive system only the non reactive couples can be used for binary measurements.\textsuperscript{112} Thus, for these systems the description of the multicomponent equilibria is intrinsically uncertain. In fact, the prediction of the multicomponent equilibria discussed in this section and of the reaction rate (next section) affect each other. In other words, the reaction rate must be regarded as the result of the choice of a particular multicomponent competitive adsorption model.

### 7.1.1 Multicomponent equilibria

The rigorous description of the adsorption and swelling on polymer particles is based on the Flory-Huggins model. This model has been used to describe both the swelling dynamics\textsuperscript{113} and the selective sorption from mixtures of solvent\textsuperscript{58} and diluted systems.\textsuperscript{114} The equilibrium conditions are obtained by imposing the same activity in the liquid and in the polymer phase, i.e.:

\[ a_i^P = a_i^L. \] (7.1)

The activity of component \( i \) in the liquid phase is predicted with the UNIFAC approach.\textsuperscript{115} Since the UNIFAC approach is computationally demanding, some authors suggest to use a multicomponent Wilson model whose parameters are fitted to the results of the UNIFAC model.\textsuperscript{116} The calculations reported in the following use the UNIFAC model, although similar results might be obtained with the Wilson model. For the calculations of the batch and fixed bed reactors the advantage of the Wilson model is small. However, it could lead to a major decrease in the computational time required for an SMB model.

On the other hand the resin is considered as a gel phase enclosed in an elastic structure and therefore the activity in the polymer phase in calculated with the Flory-Huggins model:

\[ \ln a_i^P = 1 + \ln \nu_i - \sum_{j=1}^{N+1} m_{ij} \nu_j + \sum_{j=1}^{N+1} \chi_{ij} \nu_j - \sum_{j=1}^{N+1} \sum_{k=1}^{j-1} m_{ik} \nu_j \nu_k \chi_{kj} + \eta V_i \left( \frac{5}{3} \nu_p^{1/3} - \frac{7}{6} \nu_p \right) \] (7.2)

where \( \nu_i \) and \( \nu_p \) are the volume fractions of the \( i \)th component and of the polymer in the polymer phase (see notation for other symbols). The terms on the right hand side of Eq (7.2) represent the entropic and enthalpic contributions due to mixing, except the last term, which is the elastic contribution. This can be expressed in different forms depending on the length of active elastic chains.\textsuperscript{117,118} In practice the application of the Flory-Huggins model gives good results for non-functionalized resins while is cumbersome for resins where ionic
interactions play an important role. In these cases either the ionic interactions are described by adding additional parameters to Eq (7.2) or their effect is lumped into the parameters of Eq (7.2). When this is done, the Flory-Huggins model becomes an empirical tool to describe equilibrium data and its parameters have no physical meaning.

Although the approach based on the Flory-Huggins model has provided good results in the study of the esterification of acetic acid with ethanol, in this work a different approach is adopted. An empirical multicomponent Langmuir model based on activities predicted from the UNIFAC model is used to calculate the amount adsorbed on the polymer phase, i.e.:

$$n_i = \frac{\Gamma_i \infty k_i a_i^L}{\sum k_j a_j^L},$$

(7.3)

where $\Gamma_i \infty$ is the saturation capacity for component $i$. At ambient temperature these are found to be: $\Gamma_A=4.32$, $\Gamma_B=9.28$, $\Gamma_C=3.23$, $\Gamma_D=26.2 \times 10^{-3}$ mol/cm$^3$. The $k_i$ parameters are obtained from binary experiments for the couples water-methanol, water-acid and acid-methylacetate. As a reference, $k$ for water is set to 1.

The behavior of the binary system water-acid is regular and it is well described over the whole mole fraction range by the Langmuir model as shown in Figure 7.1. The selectivity for the system water-acid is high, as indicated by the large bell-shape distribution of the experimental points. The water uptake is strong because of the hydration of sulfonic groups.
The water-methanol curve exhibits an irregular shape. Firstly, it lays below the acid one because methanol, which is a rather small and polar molecule, exhibits an affinity toward the resin much closer to the one exhibited by water. At low water mole fractions the steepness of the XY plot indicates a high water to methanol selectivity. At high water mole fraction the selectivity approaches one. A similar azeotropic behavior has been observed for the ethanol-water system. A good description of this behavior is provided by the Flory-Huggins model as well as by a bi-Langmuir model, which requires more parameters than the Langmuir one. However, the description of the selectivity behavior over the whole range is not needed for a description of the batch, fixed bed and SMB reactors. In practice water mole fraction does not exceed 0.2 and in this concentration range the Langmuir model yields a satisfactory prediction.

In addition, a detailed description of the low water mole fraction region is needed to predict the performance of the reactor in the desorption runs. The steepness in the origin of the XY diagram qualitatively indicates that large amounts of solvents are required to desorb small traces of water from the resin. On the one hand this is desired for the removal of water from organic mixtures which is the usual applications of resins such as Amberlyst, on the other hand this is a problem in reactive chromatography which calls for a better catalyst design.

Finally, the system methylacetate-acetic acid is studied to complete the fitting of the thermodynamic parameters. Similar results as those of Figure 7.1 show that at low concentrations the selectivity of this system is about 10 ($k_D = 0.06$), which is in agreement with the previous results for the system acetic acid-ethylacetate. The low selectivity exhibited by the ester is due to its low polarity.

The different selectivity between the reactions products, namely water and ester, is exploited to enhance conversion in the fixed bed during the transient and in the SMBR through the chromatographic effect.

### 7.2 Batch reactor

At ambient temperature, the reaction rate in the homogeneous liquid phase is negligible when compared to the reaction rate measured in the presence of the resin. Several runs at different initial compositions and different amounts of liquid phase and resin have been run to characterize the kinetic behavior of our system. A typical result from a reaction run is shown in Figure 7.2. The mole fraction profiles of the reactants decrease while the ester and water are formed. As a result of the selective water uptake of the resin, the water mole fraction in the liquid phase is always lower than the ester one, even though the products are
produced in stoichiometric amounts.

Figure 7.2: experimental and predicted behavior of batch esterification of methanol and acetic acid. 
a) initial methanol volume 86 ml, initial acetic acid volume 44 ml. Amberlyst 15 weight: 9 g. b) initial methanol volume 15 ml, initial acetic acid volume 115 ml. Amberlyst 15 weight: 9 g. Solid line: model. Symbols: ○ methanol, □ acid, △ methylacetate, ▽ water.

The mole fraction profiles are described with the following batch reactor model:

\[
\frac{d(V_Lc_i)}{dt} + \frac{d(V_pn_i)}{dt} = \nu_i r \tag{7.4}
\]

\[
\frac{dn_i}{dt} = k_m (n^*_i - n_i) + \nu_i r \tag{7.5}
\]

The liquid phase is assumed ideal, i.e. \( \sum c_i \tilde{V}_i = 1 \), and the polymer is allowed to swell according to:

\[
V_p = V_p^{dry} + \sum_{i=1}^{N} n_i \tilde{V}_i. \tag{7.6}
\]

Since the reaction is taking place in the adsorbed phase, the following second order model is adopted:

\[
r = k_f n_An_B \left( 1 - \frac{n_C n_D}{n_An_B K_{eq}} \right) \tag{7.7}
\]

Let us note that using the parameters estimated in the previous section the product of the adsorbed phase concentrations in the second term of this reaction rate model is approximately
equal to the product of the activity coefficients, that is \((n_{CN_D})/(n_{AN_B}) \approx (a_{CN_D})/(a_{AN_B})\), and therefore Eq (7.7) is also thermodynamically consistent.

The parameters of the model are \(k_m\), \(K_{eq}\) and \(k_f\). On-line measurements of uptake of small amounts of water from a resin equilibrated with methanol yield a characteristic time of adsorption on the order of half a minute. Experiments at different mixing velocities indicates that the main mass transfer resistance is within the particle. Therefore in the following simulations \(k_m = 4 \text{ min}^{-1}\) has been used for all the species.

The \(K_{eq}\) obtained from literature is equal to 32. This indicates that the reaction equilibrium is strongly shifted toward the synthesis of the products.

With these values, the forward reaction rate is found to be \(300 \text{ gr} / (\text{min} \cdot \text{mol})\). This value is similar to the one obtained previously for the ethylacetate synthesis. Since the characteristic time of reaction is much larger than the time of adsorption, the kinetic value fitted is independent of the \(k_m\) adopted. In other words, an equilibrium model would yield the same results. This point is further proved by other runs where catalysts of different particle sizes have been used. The change in the particle size has no effect on the dynamics of the batch esterification thus showing that the catalyst works in the chemical regime.
Finally, the reaction in Figure 7.3 has been repeated twice, starting both with the resin equilibrated with pure acid and pure methanol. The difference in the resin swelling (about 30% higher using methanol) could suggest a smaller mass transfer coefficient in the first run. However, the results of the two runs are identical, thus showing again that the time needed to achieve equilibrium is much shorter than the characteristic reaction time. These results prove that in our case the dynamics of the batch reactor is controlled only by the reaction rate. Let us notice that this conclusion, which is in agreement with previous data, is not general and does not extend to faster reactions or to the same reaction at higher temperatures.

The results of Figure 7.2 show that the kinetic model is able to predict the batch reaction performance under different feed conditions without the adjustment of any parameters. The use of liquid phase concentrations in Eq (7.7) could be deceiving, since the interplay between sorption equilibria and reaction in the adsorbed phase would manifest itself as an apparent varying reaction order.120,121

Finally, the reliability of the model has been checked by running an experiment for the backward reaction starting from the products. A good match shown in Figure 7.3 with the experimental results obtained without adjusting any parameters proves the consistency of the proposed model also for the backward reaction rate.

7.3 Fixed Bed Reactor

The typical behavior of the experimental concentration of the fixed bed effluent's are drawn in Figure 7.4. In this experiment, the column is initially conditioned with methanol and the feed is a mixture 25/75 molar of acetic acid and methanol. Methanol is first eluted, followed by a non-reactive transition corresponding to the breakthrough of the less retained species, methylacetate, which is produced by the conversion of the feed mixture on the catalytic bed of the column. The more retained components, acetic acid and water, are eluted through the second transition which connects the intermediate state of methanol and methylacetate with the steady state. The difference in the area of the products formed in stoichiometric amount is proportional to the difference in the amount of water and methylacetate adsorbed. This is in turn due to the different selectivity of the products for the stationary phase. As shown in Figure 7.4, in the chromatographic reactor the difference in selectivity of the products is exploited to collect only one of them (methylacetate in methanol) during the transient.

In this work, the reactor is regenerated using methanol until the initial conditions are re-established, so that the reactor is ready for a new cycle. In principle, regeneration could
be run either with acid or with methanol. However, as shown in Figure 7.1, the selectivity for the binary system water-methanol is lower and therefore regeneration with acid is not convenient since a larger number of bed volumes should be eluted. Let us notice that this is not a general conclusion. Longer alcohols with a small dipole moment may show a larger selectivity than the acid. For these systems regeneration with acid should be considered, although safety and material problems may limit the use of pure acid solutions.

The information gained in the study of the binary adsorption equilibria and the batch reactor can be used to predict the behavior of the chromatographic reactor by solving the following differential mass balance equations:

\[ \varepsilon^* \frac{\partial c_i}{\partial t} + \frac{\partial (u c_i)}{\partial z} = \varepsilon_b \frac{\partial^2 (D_{eff}(u)c_i)}{\partial z^2} - (1 - \varepsilon^*) k_m (n_i^{eq} - n_i) \tag{7.8} \]

\[ \frac{\partial n_i}{\partial t} = k_m (n_i^{eq} - n_i) + \nu_i \nu. \tag{7.9} \]

The solution of Eqs (7.8) and (7.9) is obtained with the method of lines using an up-wind
scheme with Danckwerts boundary conditions. The model equations are completed with the assumption that the mobile phase is ideal, i.e. \( \sum c_i \tilde{V}_i = 1 \).

Figure 7.5: internal profiles predicted by the model for the run in Figure 7.4. a) methanol and methylacetate mole fraction at \( \tau = 0.2 \) (solid and broken line) and at \( \tau = 0.8 \) (dotted and dash-dotted line). b) acid and water mole fraction at \( \tau = 0.2 \) (solid and broken line) and at \( \tau = 0.8 \) (dotted and dash-dotted line). c) reaction rate at \( \tau = 0.2 \) (solid line) and at \( \tau = 0.8 \) (dotted line).

Before assessing the results of the model, it is worth discussing how the parameters \( D_{\text{eff}} \), \( k_{\text{cr}} \) and \( \varepsilon \) are obtained. Moreover, the hydrodynamic regime needed to obtain reproducible experimental results shall be discussed.

The effective axial dispersion due to backmixing is estimated using the Chung and Wen relationship with an average particle diameter of 0.5 mm. Therefore diffusivity is a function of the superficial velocity, which is changing along the reactor during the transient. However, since the change in molar volume upon reaction is small, the velocity change could
be neglected without significantly affecting the shape of the effluent profiles.\textsuperscript{58}

The mass transfer parameter is assumed equal for all the species and it is fitted using the experimental breakthrough profiles. The value of 4 min\textsuperscript{-1} used in the batch experiments was found to be in reasonable agreement with all the experimental results. Although different flow rates and flow regimes (bottom-up or top-down) should require a different mass transfer parameter, the assumption of constant $k_m$ and the use of a solid film linear driving force model allow a good prediction of the experimental results.

The overall void fraction $\varepsilon^*$ is calculated by measuring the retention times of toluene pulses in the temperature range 25-65 °C. The constant retention times indicate that the adsorption of the toluene can be neglected. A value of $\varepsilon^* = 0.65$ has been found, which corresponds to $\varepsilon_b = 0.45$ when $\varepsilon_p = 0.36$. The bed porosity obtained is in agreement with the value expected for a column packed with spheres.\textsuperscript{97} The assumptions of constant void fraction and constant column length lead to a constant swelling ratio. In the experiments the column is compressed on top by a frit to reduce the extracolumn dead volume. Under these experimental conditions a column swelling of less than 5% is observed and therefore the assumption of constant swelling can be adopted to simplify the solution of the model.

Finally, let us notice that the hydrodynamic regime plays an important role on the results of the experiments. The difference in density of the species (at 25 °C 1.05, 0.77, 0.93, 1 g/ml for acetic acid, methanol, methylacetate and water) can decrease the separation efficiency. Moreover, it has been shown that this effect cannot be modeled simply by introducing an enhanced mixing term.\textsuperscript{58} The fronts traveling in the column are hydrodynamically stable, and therefore can be modeled, only when moving along the column from the bottom to the top the density profile is decreasing. In other words, in order to obtain a reproducible effluent profile the fronts through which density is decreasing must travel bottom-up and vice versa. Since the feed has a higher density than methanol, in the reactive runs the flow is is bottom-up in order to obtain consistent results, while in regenerations is top-down.

The model results are in good agreement with the composition of the fraction collected at the reactor outlet for the conditions of Figure 7.4, where a rather dilute feed mixture is fed. The model predicts well the breakthrough times of the fronts and the values of the plateaus. As the fronts travel inside the column from the bottom to the top an increasing density profile is established, thus the correct hydrodynamic regime has been adopted. The internal profiles of concentration and reaction rate calculated at different times are reported in Figure 7.5. In Figure 7.5a and 7.5b the profiles of methanol and methylacetate and water and acetic acid are drawn at different times. It is worth noticing that the methylacetate travels ahead of the water and acetic acid front due to its low retention on the resin. This
front is non reactive and corresponds to the first transition in Figure 7.4. On the other hand, Figure 7.5b shows clearly that the acid and water fronts travel together. In the absence of reaction, the velocity of these two fronts are different since the selectivity for the resin is higher for water as shown in Figure 7.1. However, the reaction couples the fronts together since as acid travels ahead of the water front, it immediately reacts with methanol to form water.

Figure 7.6: experimental and predicted effluent profiles for Amberlyst 15 catalyzed esterification of methanol and acetic acid in fixed bed reactor. Acid/methanol feed mole ratio 50/50. Operating conditions: column length 22.7 cm, column diameter 1.6 cm, bottom-up flow, flow rate 0.5 cm³/min. Initial condition: methanol. See Figure 7.4 for notation.

The reaction rate drawn in Figure 7.5c shows a peculiar shape since the profiles are the results of two different contributions. On the one hand, the integration of the model equations at steady state gives a decreasing profile. The steady state profile is the envelop of the profiles taken at different times and it smoothly decreases along the reactor. On the other hand, there is a reaction rate peak travelling with the front through which water and acetic acid break through. At the time $\tau = 0.2$ and $\tau = 0.8$ this peak can be clearly seen at a dimensionless axial coordinate of about 0.2 and 0.7, respectively. At the end of the transient, the reaction rate profile is monotonically decreasing but, as suggested by Figure 7.5c, the reaction rate is positive over the whole reactor length, thus showing that the steady state conversion achieved in this run is below the equilibrium value. In fact, the achievement of equilibrium conditions would correspond to the achievement of a zero reaction rate before
the column outlet. As a consequence, in this example a smaller flow rate would increase the steady state conversion.

![Graph](https://via.placeholder.com/150)

**Figure 7.7:** experimental and predicted effluent profiles for Amberlyst 15 catalyzed esterification of methanol and acetic acid in fixed bed reactor. Acid/methanol feed mole ratio 74/26. Operating conditions: column length 22.7 cm, bottom-up flow, flow rate 0.2 cm³/min. Initial condition: methanol. Solid line: model. See Figure 7.4 for notation.

The increase of the acid in the feed concentration to a molar ratio of 50/50 does not change qualitatively the breakthrough profiles, as shown in Figure 7.6. However, it is worth noting that this change leads to a peak in the breakthrough profile of the methanol in proximity of the reactive front. This behavior has already been reported in the study of a similar system and a physical explanation has been provided. It suffices here to notice that this behavior, which is clearly seen both in the experiments and in the model, is a sign of the transition of the reactor between two regimes that are quantitatively very different. In fact, a further increase in the feed concentration leads to the profiles shown in Figure 7.7. Here, the initial methanol state is followed by a first transition where methylacetate is breaking through as before. However, a second intermediate state rich in acetic acid and where undetectable amounts of methanol are collected is realized between the methylacetate rich state and the steady state. Thus in this example, three transitions are separating the four different intermediate states.

The profiles in Figure 7.8a can be useful to interpret the dynamic behavior seen in Figure 7.7. At the beginning of the run ($\tau = 0.3$) the reaction rate is developing its steady state
profile in the neighborhood of the reactor entrance with a peak traveling on it. This peak is located at the maximum methylacetate concentration and at the acid front (dimensionless length of about 0.3). For longer times ($\tau = 0.8$) the acid rich intermediate state is developed and two peaks are traveling. The smaller one is located at a dimensionless length of 0.6 and travels together with the transition that connects the intermediate acid rich state and the steady state. The large peak travels with the transition connecting the methylacetate rich state with the acid rich state. It is worth noticing that both the steady state and the intermediate acid rich state are equilibrium states and no reaction is taking place.

The methanol concentration in the acid rich state is smaller than the steady state value.
In fact, the steady state equilibrium conversion is obtained from the integration of the concentration profiles from the feed value until reaction rate goes to zero when equilibrium is achieved. However, the acid front traveling in the column displaces methanol ahead and allows to achieve an intermediate state in the transient where methanol concentration is smaller than steady state.

![Graph showing effluent profiles](image)

**Figure 7.9:** experimental and predicted effluent profiles for column regeneration using methanol. Operating conditions: column length 22.7 cm, column diameter 1.6 cm, top-down flow, flow rate 0.5 cm\(^3\)/min. Initial condition: steady state operation for the run in Figure 7.6. See Figure 7.4 for notation.

Finally, a regeneration run is shown in Figure 7.9. The reactor is regenerated with methanol after the run in Figure 7.6. Before flushing methanol, the flow direction has been changed from bottom-up to top-down. The density profile calculated in Figure 7.9 confirms that the correct density profile is established in the column. The change in the flow direction has an impact on the outlet profiles. At the beginning the fraction collected during regeneration correspond to the concentration established at steady state near the inlet of the column during reaction. Therefore the concentration of the reactants is high while the concentration of the products is low. As a result, the concentration of acid is decreasing and the concentration of methylacetate is first increasing then decreasing.

The behavior of water is more complex due to the peak which is the result of the displacement caused by methanol. The desorption front of water exhibits a long tail. In fact, the selectivity of the system water-methanol is increasing when the mole fraction of water decreases, as
shown by the steepness of the mole fraction plot in Figure 7.1. Thus, a complete removal of water from the reactor is difficult and requires large amounts of methanol (more than 2 bed volumes). Adsorption measurements not reported here show that this problem cannot be overcome by increasing the temperature and that a better design of the resin is needed for an improvement. Let us notice that the model developed here, which nicely predicts the adsorption runs and desorption tail, can be a useful tool to optimize the methanol requirement for the continuous operation of the process using a Simulated Moving Bed reactor.
Chapter 8

Analysis of Simulated Moving Bed reactors

In this chapter we deepen the understanding of the behavior of the SMBR process through a modelling analysis. In particular we develop a procedure to identify the optimal operating conditions for SMBRs and we illustrate it for a model system, namely the esterification of acetic acid and ethanol catalysed by Amberlyst 15. Acetic acid (A) and ethanol (L) are fed between section 2 and section 3, while ethanol itself is used as eluent and supplied at the bottom of section 1. It is shown that when the operating conditions are properly chosen, acetic acid is completely converted and the two products, i.e. ethyl acetate (P) and water (W), are collected in the raffinate and extract, respectively, both diluted in ethanol.

The results of the simulations are reported in terms of the flow rate ratios $m_j$ (1.7) which control the separation in non reactive SMBs. These dimensionless groups bring together the relevant process parameters, i.e. flow rates $Q_j$, switch time $t^*$, column volume $V$ and overall bed void fraction $\epsilon$. The objective of this analysis is to determine a region in the space spanned by the four flow rate ratios where complete conversion of acetic acid and complete separation of products is achieved. The adopted procedure is based on the knowledge of the triangle-shaped region of complete separation which characterises non-reactive SMBs. In addition the effect of feed composition is studied and some data reported earlier in the literature are explained.
8.1 Modeling Simulated Moving Bed Reactors

The behaviour of the single isothermal chromatographic reactor, which corresponds to each single column of the SMBR unit in Figure 1.2, is described by means of the equilibrium-dispersive model, where local phase equilibrium between the mobile and stationary phase and finite reaction rate are assumed.\(^{58}\) Mass balance equations for each component \(i\) are written as follows:

\[
\varepsilon \frac{\partial c_i}{\partial t} + (1 - \varepsilon) \frac{\partial n_i}{\partial t} + u \frac{\partial c_i}{\partial z} = \varepsilon D \frac{\partial^2 c_i}{\partial z^2} + \nu_i (1 - \varepsilon) R \quad (i = A, L, P, W) \tag{8.1}
\]

and must be solved together with initial and boundary Dankwerts conditions (note that \(\nu_P = \nu_W = 1 = -\nu_A = -\nu_L\)). The dispersive term, which is assumed to be the same for all species, is accounted for through the numerical solution of the model by properly tuning the number of grid points.\(^{54}\) With a backward finite difference scheme the number of grid points \(N_G\) and the diffusion coefficient of Eq. (8.1) are related through the following equation:

\[
N_G = \frac{Lu}{2\varepsilon D} \tag{8.2}
\]

A number of grid points \(N_G = 60\), which is realistic for SMB applications,\(^{32}\) is used in all simulations.

The reaction is catalysed by the acid groups of the resin and takes place in the polymer phase. The rate of reaction is given by the following mass action law in terms of the adsorbed phase composition, \(n_i\):

\[
R = k \cdot n_A \cdot n_L \cdot (1 - \Omega) \tag{8.3}
\]

where \(\Omega = (n_P \cdot n_W) / (n_A \cdot n_L \cdot K_{eq})\).

The adsorbed phase concentration in Eqs (8.1) and (8.3) is assumed at equilibrium with the fluid phase. The thermodynamics of this system has been described using a detailed model where the activity coefficients have been evaluated with a modified Flory-Huggins and UNIFAC models for the polymer and fluid phase, respectively.\(^{112}\) Moreover, the effect of composition on the swelling of the resin has been accounted for. Although the aforementioned model has been proved to be suitable to describe the non-constant selectivity adsorption behavior of this system, in this work a simpler multicomponent Langmuir model is used:

\[
n_i = \frac{H_i c_i}{1 + b_A c_A + b_L c_L + b_P c_P + b_W c_W} \quad (i = A, L, P, W). \tag{8.4}
\]

The motivation for this choice is twofold. First this simpler thermodynamic model allows faster calculations. Secondly, it is useful to analyse the results in terms of the properties...
of non reactive SMBs, for which explicit expressions for the boundaries of the complete
separation region are available in the case of Langmuir adsorption equilibria.\textsuperscript{33,37} In addition,
when properly adjusting the values of the model parameters in Eq. (8.4), this gives results
very similar to those of the previous model.

The thermodynamic parameters reported in Table 8.1 have been estimated from the binary
adsorption data for the non-reactive couples, while the kinetic parameters have been fitted
considering batch experiments, as discussed earlier by Mazzotti et al. (1996), yielding
\( k = 41.32 \text{ cm}^3/(\text{mol}-\text{sec}) \) and \( K_{\text{eq}} = 2.36 \). Finally, it has been observed experimentally
that under the operating conditions of the SMBR, minor changes of the swelling ratio occur
since the adsorbed phase concentrations of ethanol and water, which yield high swelling,
are always much larger that those of the other components, which yield small swelling.
Accordingly an average value of the bed void fraction \( \varepsilon = 0.6 \) has been adopted. The
reliability of this empirical model has been tested by comparing single column experiments
with numerical simulations, when different mixtures of acetic acid and ethanol are fed to
columns initially saturated with ethanol. A satisfactory agreement between model results
and experimental data\textsuperscript{58} has been found in all examined cases.

### 8.2 Parametric analysis of SMBR performances

The aim of this section is to determine the region in the operating parameter space where
complete conversion of the limiting reactant, i.e. acetic acid, and complete separation of the
products is achieved. The existence of this region is conjectured based on analogous results
obtained for non reactive SMBs and its determination is based on the following observation:

- Sections 1 and 4 (see Figure 1.2) are regenerating sections where under complete
  conversion/separation conditions no reaction occurs. Therefore we can apply the same
criteria as for non-reactive SMBs, i.e. \( m_1 \) and \( m_4 \) must be larger and smaller than the
corresponding critical values which guarantee regeneration of the adsorbent and the

\[
\begin{array}{|c|c|c|c|c|}
\hline
 & A & L & P & W \\
\hline
H_i & 1.90 \cdot 10^2 & 1.17 \cdot 10^3 & 1.50 \cdot 10^1 & 1.14 \cdot 10^4 \\
b_i \text{ cm}^3/\text{mol} & 5.43 \cdot 10^4 & 2.13 \cdot 10^5 & 10^4 & 5.92 \cdot 10^5 \\
H_i^* & / & / & 4.09 \cdot 10^{-3} & 3.13 \\
\hline
\end{array}
\]

Table 8.1: ethyl acetate synthesis on Amberlyst 15. Thermodynamic parameters for the Langmuir
model (8.4) and pseudo-Henry constants (8.5).
eluent, respectively. Once these conditions are fulfilled, the specific values of \( m_1 \) and \( m_4 \) have no effect on the SMBR performance in terms of conversion and purity.\(^{33}\)

- If \( m_1 \) and \( m_4 \) are properly selected as indicated above, the dimensionless flow rate ratios \( m_2 \) and \( m_3 \) determine the separation performance. The complete conversion/separation region can be represented in the \((m_2, m_3)\) plane, and its shape and location depend on the feed composition (Mazzotti et al. 1997c).

- The switch time has an important role in determining process performances, since it affects column efficiency. In addition, in the case of SMBRs there is a lower bound for \( t^* \), below which the residence time in the reactive zone of the SMBR is too small to allow the reaction to occur to any significant extent.

- The location of the complete conversion/separation region can be determined by performing simulations along lines parallel to the diagonal of the \((m_2, m_3)\) plane, i.e. by crossing the region itself.\(^{45}\)

Simulations at different values of \( Q_2 \) and \( Q_3 \), keeping constant values of \( Q_1, Q_4 \) and \( t^* \) have been performed, namely \( Q_1 = 12.5 \text{ cm}^3/\text{min}, Q_4 = 0.575 \text{ cm}^3/\text{min} \) and \( t^* = 600 \text{ s} \). The geometric parameters are: \( A = 3.42 \text{ cm}^2, L = 14 \text{ cm} \) and \( \varepsilon = 0.6 \). From Eq. (1.7) one obtains \( m_1 = 5 \) and \( m_4 = -1.2 \), which fulfil their relevant constraints. The values of \( Q_2 \) and \( Q_3 \) are chosen in such a way that the corresponding operating points in the \((m_2, m_3)\) plane move along straight lines at different distance from the diagonal. This allows us to determine not only the position but also the shape of the complete conversion/separation region.

An indication about the location of the region of complete conversion/separation may be obtained by considering the case when the feed is constituted of acetic acid infinitely diluted in ethanol, so that the chemical reaction reaches equilibrium instantaneously and axial dispersion is negligible.\(^{122}\) In these conditions \( c_L = 1/\rho_L \), and the concentrations of all the other species can be neglected. The reaction products exhibit linear adsorption equilibria according to the following relationship:

\[
\frac{n_i}{c_i} = \frac{H_i}{1 + b_L/\rho_L} = H_i^* \quad (i = P, W). \tag{8.5}
\]

In this case the region of complete conversion/separation is the square triangle with dashed boundaries shown in Figure 8.1, given by \( m_2 = H_{p}^* \) and \( m_3 = H_{w}^* \), which corresponds to the region of separation for a non reactive SMB unit where only the separation of the two products is performed.
8.2 Parametric analysis of SMBR performances

Figure 8.1: ethyl acetate synthesis on Amberlyst 15. SMBR performances for a 40/60 acetic acid to ethanol feed ratio in a set of operating points: (●) complete conversion and 100% purity of the outlet streams; (○) incomplete conversion of acetic acid, which pollutes at least one of the outlet streams. The square triangle with dashed boundaries corresponds to the complete conversion/separation region for a feed ratio of 0/100 (see text).

Two sets of simulations have been performed at different feed compositions. The results are illustrated in Figures 8.1 and 8.2 for an acetic acid to ethanol feed ratio of 40/60 and 100/0, respectively. Four sets of operating points lying on straight lines at increasing distance from the diagonal are considered in each figure. Different symbols refer to different process performances: (●) indicates complete conversion of acetic acid and 100% purity of the products streams ($P_E = c_W^E / (c_W^E + c_W^F)$ and $P_R = c_W^R / (c_W^R + c_W^F)$), (○) indicates that some unreacted acetic acid is still present at least in one of the product streams. Note that since the reaction is reversible, whenever either both reactants or both products are present, then all four components are present. Figures 8.1 and 8.2 show that the complete conversion/separation region, i.e. the region which contains all black circles, has a triangular shape as in the case of non reactive SMB. Similar is also the unit behavior for operating points outside the triangle: the unreacted acetic acid ends up in the raffinate or in the extract, depending on whether the corresponding operating point is located to the right or to the left hand side of the triangle, respectively.

The two approximated regions at 40/60 and 100/0 acetic acid /ethanol ratio are compared in Figure 8.3, where also the region of complete conversion/separation corresponding to
infinite dilution of acetic acid in the feed stream is shown. It appears that as the acetic acid in the feed increases the region of complete conversion/separation shrinks and the distance of its vertex from the diagonal becomes smaller. Let us consider the simulations above with respect to the productivity per unit mass of resin:

\[
PR = \frac{(Q_3 - Q_2) c_A^* M_A}{V \rho_p (1 - \varepsilon) N_C} = \frac{(m_3 - m_2) c_A^* M_A}{t^* \rho_p N_C}.
\]  

(8.6)

Accordingly, for a given composition, points further away from the diagonal in Figures 8.1 and 8.2 achieve a better productivity. In particular, the largest productivity is obtained in the two points of complete conversion on the third straight line from the diagonal in Figure 8.1 and on the second one in Figure 8.2. The largest productivity values for each feed composition are summarised in Table 8.2, together with the corresponding values of \((m_2, m_3)\); at infinite dilution \((m_3 - m_2)_{\text{max}} = H^*_W - H^*_P\) (see Table 8.2). Since productivity is given by Eq. (8.6) as the product of two quantities, i.e. \((m_3 - m_2)\) and \(c_A^*\), which monotonously decrease and increase, respectively, when the fraction of acetic acid in the feed increases, its non monotonic behavior is not surprising. These results lead to the conclusion of general validity that an optimal acetic acid to ethanol feed ratio exist and provide useful guidelines for process optimisation.
8.2 Parametric analysis of SMBR performances

Figure 8.3: ethyl acetate synthesis on Amberlist 15. Comparison of the approximate regions of complete conversion/separation at different acetic acid to ethanol feed ratio: (- - -) 0/100; (- - -) 40/60; 100/0 (—).

8.2.1 Effect of flow rates and switch time

The results of the analysis above are compared with the data reported by Ching and Lu\textsuperscript{123} for the inversion of sucrose to fructose and glucose in a 3 section SMBR (without eluent recirculation from section 3). The adsorption of fructose and glucose is described by a linear isotherm, while sucrose is non adsorbable, i.e. $H_f = 0.65$, $H_g = 0.45$ and $H_s = 0$. The smallest value of $m_1$ used in the simulations is 1.67, which is larger than the critical value 0.65, hence complete regeneration in section 1 is always achieved: therefore the performance of the unit depends only on the position of the operating point in the plane ($m_2$, $m_3$).

The simulations reported by Ching and Lu (1997) correspond to different operating points in the ($m_2$, $m_3$) plane, as illustrated in Figure 8.4, where also the complete conversion/separation linear triangle is shown (note that the latter has been calculated assuming no reaction and therefore represents an approximation of the actual complete conversion/separation region).

It is worth noticing that in the non reactive case the region on the left of the square triangle ($m_2 < H_f$, $H_g < m_3 < H_f$) corresponds to pure raffinate only; the region above ($H_g < m_2 < H_f$, $m_3 > H_f$) to pure extract only; finally the region when $m_2 < H_g$ and $m_3 > H_f$ leads to both components distributed in the two product streams. Note that operating points on the AB segment correspond to constant flow rates and different switch time,
While points on CD and EF correspond to the same value of switch time but different flow rates. In the first case $Q_2$ and $Q_3$ are changed while keeping the feed flow rate constant, whereas in the second case the feed flow rate, and therefore $Q_3$, is increased keeping $Q_1$ and $Q_2$ constant. As shown in Figure 8.4, the operating points along AB and CD are very close in the $(777,2,777,3)$ operating parameter plane even though they have been obtained using rather different values of flow rates and switch time.

The purities calculated by Ching and Lu (1997) in the runs along AB are shown in Figure 8.5. It is observed that, as the switch time increases, the raffinate purity, which is initially close to 100%, drops, while the extract purity increases, even though it never reaches 100% because the line AB is too far from the diagonal. The same behavior is obtained for operating points along CD when changing the flow rates values. In the case of runs along EF similar results in terms of raffinate purity are obtained, whereas extract purity does not improve much. Although the last two cases are not shown here for brevity, it is remarkable that all the above results are consistent with the position of the operating points in the $(m_2, m_3)$ plane and the conclusion of the analysis reported in the previous section. Better performances are predicted in an operating point within the square triangle, such as point G, where in fact purities larger than 95% have been obtained by Ching and Lu.

**Table 8.2:** ethyl acetate synthesis on Amberlyst 15. Productivity of the SMBR unit as a function of the acetic acid to ethanol feed ratio (see Eq. (8.6) for the definition).
Figure 8.4: sucrose inversion. Linear region of separation for the system glucose-fructose and operating points for the simulations. The following geometric parameters have been used: $A = 22.9$ cm$^2$, $L = 75$ cm and $\varepsilon = 0.4$.

Figure 8.5: purity performances for the runs along line AB of Figure 5, as reported by Ching and Lu (1997).
Chapter 9

Concluding remarks

This thesis provides a new tool which allows to extend the Equilibrium theory approach for the design of binary countercurrent adsorptive separation units to a larger class of isotherms. This conclusion is particularly important in view of the wider and wider application of continuous chromatography, through the Simulated Moving Bed technology, in the fine chemical and pharmaceutical industry. Using as examples the bi-Langmuir isotherm and the IAS model, a general mathematical procedure is illustrated which can be applied also to other isotherms. Some calculations show how the procedure described above can be used to analyze in a rather straightforward way important aspects of the continuous chromatography technology, including the effect of feed composition. A simplified procedure which allows to reduce the mathematical complexity of the involved calculations leading only to explicit algebraic relations, without significantly affecting the accuracy of the final results, is presented. This short-cut procedure can be implemented experimentally to reduce considerably the amount of experiments required to determine the optimal separation conditions.

Before analyzing the experimental results, the non-ideal effects are studied. A well known problem of small scale SMB units made of a series of individual chromatographic columns is the presence of dead space between the fixed beds, whose volume, though minimized, can be comparable to the column volume. In this case the role of extracolumn dead volume can neither be neglected nor be considered simply as a further source of uncontrollable axial dispersion in the unit. It is shown that the increase the residence time of the composition fronts in the chromatographic module made of the dead volume and the chromatographic column can be exactly accounted for and compensated through an extension of the so called "Triangle Theory" previously developed in the frame of Equilibrium Theory for the robust design of the operating conditions of SMB units.

The design of the optimal operating conditions of simulated moving bed units in the pres-
ence of non-negligible dispersive effects, i.e. axial mixing and mass transfer resistances, has been considered. This has been done using an equilibrium-dispersive model of SMB units, which is detailed enough to properly account for the mentioned effects and simple enough to allow for massive numerical computations. The outcome of this analysis demonstrates the usefulness of the ideal prediction of the complete separation region in the operating parameters plane obtained through Equilibrium Theory, i.e. assuming infinite column efficiency. The effect of dispersive phenomena on the shape of the complete separation region and the location of the optimal operating point have been quantitatively elucidated. It is found that, when considering values of axial dispersion and transport resistances which are typical in applications, the changes of the separation regions, with respect to the predictions of Equilibrium Theory, are relatively small. Nevertheless they cannot be neglected in the quantitative evaluation of process performances, where even differences of less than 1% in product purity may be quite critical. Although the analysis has been performed with reference to a specific system, as it is necessary when a numerical approach is adopted, its results bear a more general qualitative validity. One aspect particularly relevant for applications is the behavior of SMBs in terms of purity of the outlet streams and productivity. An asymmetric behavior with respect to the more and less retained component to be separated has been evidenced. This must be taken into account and exploited in order to select not only optimal operating conditions, but also stationary and mobile phases, i.e. elution order of the components to be separated. The value and usefulness of the theoretical analysis on extracolumn dead volumes and non-ideal effects has been proved by discussing and explaining a set of experimental results in the literature.

After the analysis of nonideal effects, the short-cut technique to design SMB separations under nonlinear conditions is discussed. This allows to approximate the region of separation based on the Equilibrium Theory model using a few experiments requiring only a small amount of pure products. First of all, pulses under dilute conditions allow the Henry constants to be calculated; these are then used to design the separation under linear conditions, as well as operating conditions for the regenerating sections. The information needed to draw the approximate regions of complete separation under nonlinear conditions is provided by adsorption/desorption runs at the concentration of the feed mixture and pulse experiments on a column loaded only with the more retained enantiomer.

The procedure is applied to the study of the resolution of the Tröger’s base enantiomers on CTA; this is a rather difficult separation due to the low column efficiency. The experimental SMB runs at increasing feed concentration show how the nonlinear adsorption behavior affects the shape and the positions of the region of complete separation by shifting its optimal point toward lower \( m_2 \) and \( m_3 \) values in the \((m_2, m_3)\) plane. The experiments also
show that the separation performance of a small scale SMB unit are very sensitive to the operating conditions. Changes in the switch time of one minute or less can lead to significant changes in the product purity. Therefore, the rational interpretation of the experimental results provided by this analysis is useful to reduce the number of experiments needed to optimize the operating conditions, particularly for a new separation without the detailed and lengthy measurement of the competitive adsorption isotherms.

In sum, the results presented in this part of the thesis allow to calculate the separation region for a new binary separation with a small number of experiments. It is shown with reference to the Tröger's base system, how nonideal effects can be accounted for in the development of a new chiral separation. Moreover, the insights of the theoretical analysis allow to optimize the operating conditions for a separation where only one component is needed pure. This case has great practical importance since SMB must not be considered as a stand alone unit operation, but its optimal operating conditions are the result of integration with downstream processes, such as crystallization and racemization. Finally, the procedure developed allows to investigate new ways of optimizing SMB technology, such as the use of temperature gradients. The development of these tools is important to foster the application of SMB toward more and more complex applications in the field of bio, food and pharmaceutical industry. Other important directions for further investigations are the application to multicomponent separations and new ways of managing the column switch to reduce solvent consumption and increase product purity.

The second part of the thesis focuses is on the application of SMB technology to reactive chromatography. A small amount of experimental data on reactive chromatography is available and chemical industry has been cautious to establish this technology as a standard operation. This is primarily due to the fact that detailed understanding of SMBR still has to be achieved. Accordingly, simple criteria have not yet been introduced to define operating conditions needed to accomplish required process specifications in terms of productivity and product purity. This part of the thesis is directed toward further deepening the understanding of the behavior of SMBR units, especially their response in terms of process performance to changes in the operating conditions, such as feed composition and flow rates.

Accordingly, reliable models for numerical simulation have to be developed to enable a systematic parameter analysis of SMBR performance and a closer look at the complex interactions between the involved multicomponent sorption equilibria, chemical reaction kinetics and equilibria as well as mass transport phenomena is needed. Two model have been developed and assessed.

Firstly, the lipase catalyzed esterification of 2-ethyl-1,3-hexanediol and propionic acid in
hexane, which leads to the formation of a primary monoester with high selectivity, is considered. Secondly, the esterification of methanol and acetic acid on Amberlyst 15 is studied. The two systems are representative of a large class of reactions, i.e. enzyme catalyzed esterifications and acid ion-exchange resin esterifications. Therefore the model proposed and the analysis of the dynamic behaviors of batch and fixed bed reactors are indeed general and can be applied to study a broader range of reactions.

In the last chapter, the performance of SMBRs is analyzed with reference to the flow rate ratios $m_j$, which are the key operating parameters in the case of non reactive SMBs. The results obtained through simulations with a realistic model for the ethyl acetate synthesis on Amberlyst 15 have been analyzed. It is concluded that the complete conversion/separation region in the operating parameter space has a triangular shape similar to that found for non reactive SMBs. The feed concentration has an effect at least as important as in the non reactive case. Therefore it is a key optimization parameter. The proposed approach provides insight into process behavior and guidelines for process optimization, as it has been illustrated using data relative to the inversion of sucrose to fructose and glucose. It is shown how variations in process efficiency due to changes in the operating parameters can be quantitatively described. Thus, progress towards a framework for sound interpretation of the performance of SMB units with simultaneous chemical reaction has been achieved. These results will be helpful to guide further experimental investigations and to assess the cost of downstream recovery of the solvent. The latter has a large impact on the economics of the process and it is expected that improvements in the design of the resins and in the optimization of process performance will lead to the establishment of this technology.
Chapter 10

Notation

\( a_i \) adsorption equilibrium constant in bi-Langmuir isotherms
\( b_i \) adsorption equilibrium constant in bi-Langmuir isotherms
\( c_i \) fluid phase concentration of species \( i \)
\( D \) pure eluent state
\( f \) net flux of mass
\( h \) constant linear term in the modified Langmuir model
\( H_i \) Henry constant of species \( i \)
\( K_{j}^i \) dissociation constant for formation of dead end complex with species \( j \), mol/L
\( K_{j}^m \) Michaelis-Menten constant for species \( j \), mol/L
\( m_j \) mass flow rate ratio in section \( j \)
\( \bar{m} \) modified flow rate ratio
\( M_j \) intermediate state of sections 2 and 3
\( N \) saturation capacity in the Langmuir model
\( n_i \) adsorbed phase concentration of species \( i \)
\( Q \) volumetric flow rate
\( r \) reaction rate, mmol/(g \cdot h)
\( r_{m} \) water dependent reaction rate coefficient, mmol/(g \cdot h)
\( t^* \) switch time in a SMB unit
\( V \) volume of the column
\( V_D \) extracolumn dead volume
\( x \) dimensionless column coordinate, \( x = z/L \)
\( z \) column coordinate
Greek letters

\( \alpha \) fluid state leaving section 2 in TCC unit
\( \beta \) fluid state entering section 3 in TCC unit
\( \beta_k \) substantial derivative along a \( \Gamma \) transition
\( \bar{\beta}_k \) substantial derivative along a \( \Sigma \) transition
\( \gamma \) solid state leaving section 3 in TCC unit
\( \gamma_i \) adsorption equilibrium constant in bi-Langmuir isotherms for species \( i \)
\( \Gamma \) simple wave locus in the hodograph plane
\( \delta \) fluid state entering section 2 in the 4 section TCC unit
\( \delta_i \) adsorption equilibrium constant in bi-Langmuir isotherms for species \( i \)
\( \varepsilon \) solid state entering section 3 in the 4 section TCC unit
\( \varepsilon^* \) overall void fraction of the bed, defined as \( \varepsilon^* = \varepsilon_b + (1 - \varepsilon_b)\varepsilon_p \).
\( \varepsilon_b \) bed or interpartical void fraction
\( \varepsilon_p \) intrapartical void fraction
\( \lambda \) speed of characteristic of a simple wave in the \((\tau, x)\) plane
\( \tilde{\lambda} \) speed of a shock in the \((\tau, x)\) plane
\( \sigma \) slope of characteristic of a simple wave in the \((\tau, x)\) plane
\( \tilde{\sigma} \) slope of a shock in the \((\tau, x)\) plane
\( \Sigma \) shock locus in the hodograph plane
\( \tau \) dimensionless time, \( tQ_S/V \)
\( \zeta \) local slope of a \( \Gamma \) locus in the hodograph plane
\( \phi \) fluid state leaving section 3 in the 2 section TCC unit
\( \psi \) solid state leaving section 2 in the 2 section TCC unit
\( \Psi \) excess surface potential
\( \nu_i \) stoichiometric coefficient for species \( i \)
\( \rho_a \) mass of adsorbent per unit reactor volume, g/cm\(^3\)
\( \rho_c \) mass of catalyst per unit reactor volume, g/cm\(^3\)
Subscripts and superscripts

\( a \) adsorbent
\( c \) catalyst
\( A \) more retained species in the feed
\( B \) less retained species in the feed
\( E \) extract
\( F \) Feed
\( i \) component index, \( i = A, B \)
\( j \) section index, \( j = 1, \ldots, 4 \)
\( k \) transition range, \( k = 1, 2 \)
\( R \) raffinate
\( S \) solid
\( SMB \) Simulated Moving Bed
\( TCC \) True Counter Current
\( o \) single component isotherm
Bibliography


