Enhancing the productivity of chiral multicolumn continuous chromatography intermittent simulated moving bed

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Enhancing the productivity of chiral multicolumn continuous chromatography: Intermittent simulated moving bed

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for the degree of
Doctor of Sciences

presented by
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Zurich 2011
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Shigeharu Katsuo
Dedicated to my family
Abstract

Simulated Moving Bed (SMB) chromatography is one of the key technologies to separate enantiomers and has been widely applied in the pharmaceutical, cosmetic, and food industries because of its excellent performance compared to column chromatography. Over the last decade several modified SMB schemes have been proposed in order to achieve still better productivity yet maintaining high purity of the products.

The Intermittent SMB (I-SMB) process is one of such modifications being commercialized by Nippon Rensui Corporation under the name of the Improved SMB and applied in the sugar industry. The switch time is divided into two sub-intervals; in the first step, the unit is operated as a conventional SMB, with two inlet streams (feed and desorbent) and two outlet streams (extract and raffinate), however, no flow in section four; in the second step, the inlet and outlet ports are closed and the flow is just circulated within the column train. This operation mode allows to move the concentration profiles along the columns and to adjust their relative position with respect to the outlet ports.

This thesis analyzes the I-SMB process in order to explore the potential of this technique in other application fields especially for the chiral separation. On the one hand, the theoretical study is carried out based on the equilibrium theory. Simple design criteria for the I-SMB process are derived expanding Triangle Theory for the standard SMB, and the analysis of the cyclic-steady state solutions makes clear the difference between the two processes and reveals the benefits of the I-SMB process. On the other hand, experiments as well as detail process simulations were performed in order to compare the two processes in terms of productivity and solvent consumption. Taking the separation of Tröger’s base
enantiomers on Chiralpak AD stationary phases in ethanol as a model system, it has been demonstrated that the I-SMB process provides superior performance compared to the conventional SMB under the linear as well as the nonlinear chromatographic conditions.
Zusammenfassung


Der Intermittierende SMB-Prozess (I-SMB) stellt eine dieser Varianten dar; er wurde zunächst von der Firma Nippon Rensui unter dem Namen “Improved SMB” patentiert und findet Anwendung in der Zuckerindustrie. In diesem Verfahren wird das Schaltzeitintervall (“switch time”) in zwei Schritte aufgeteilt: Im ersten Zeitschritt wird die Anlage analog zum konventionellen SMB-Verfahren betrieben, d.h. mit zwei eingehenden Strömen (Feed und Desorbent) und zwei austretenden Strömen (Extrakt und Raffinat), jedoch ohne Fluss im vierten Sektor. Im zweiten Zeitschritt werden die Ein- und Auslassöffnungen geschlossen, jedoch wird innerhalb des Säulenkreises ein zirkulierender Fluss beibehalten. In diesem Modus können sich die Konzentrationsprofile innerhalb der Säulen verschieben und ihre relative Position bezüglich der Auslassöffnungen anpassen.

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Chapter 1

Introduction

Several industries have an increasing interest in improving their access to pure single enantiomers of biologically active substances [1]. The latter often form the basis for value added products relevant for the pharmaceutical, cosmetic, and food industries. There exist two generally rivaling concepts for producing pure enantiomers. One approach is based on developing and applying enantioselective synthesis techniques, which often consist of a large number of reaction steps. Alternatively, simple non-selective synthesis can be applied in combination with advanced downstream separation techniques and recycling strategies. Crystallization and chromatography are the key technologies in the latter case, and in particular Simulated Moving Bed (SMB) chromatography is recognized as one of the attractive options to separate enantiomers [2].

SMB is a continuous multi-column chromatographic separation technique based on a countercurrent contact between the solid and mobile
1. Introduction

phases [3–5]. Approximating a true countercurrent process, True Moving Bed (TMB), the SMB simulates the rather difficult movement of the solid phase by periodic switches of all inlet and outlet ports by one column position in the direction of the fluid flow.

The SMB process was first introduced by Universal Oil Products (UOP, USA) in 1961 as a practical implementation of TMB process [6]. It has been successfully commercialized in the petrochemical and sugar processing industry and more recently in the area of chiral separations [2–5].

The use of the SMB technology for the separation of enantiomers of chiral compounds is a success story because of the ease of scaling the technique both up and down [7] and because of the excellent performance as compared to column chromatography [8]. Since chiral stationary phases (CSPs) have high efficiency, high pressure drop and high costs, still there has been a continuous effort to find modified SMB schemes that allow for higher productivity or for a smaller number of columns for the same product specifications. Such modified processes are called Varicol, where the ports are switched asynchronously [9], ModiCon, where the feed concentration is modulated during the switch interval [10], PowerFeed, where the feed flow rate is modulated [11], and FF-SMB, where the product stream is fractionated for internal re-cycling and re-feeding [12].

The Intermittent SMB (I-SMB) process is one of such modifications that has been widely applied in the sugar industry [13], but has not been considered yet for chiral separations. In the I-SMB process the switch interval is divided into two sub-intervals; in the first, the unit is operated as a conventional SMB, with two inlets (feed and desorbent) and two outlets (extract and raffinate), and zero flow rate in section four; in the second step inlet and outlet ports are closed and the internal flow through the four sections allows to move the concentration profiles
1.1 Objectives and structure of this thesis

along the columns and to adjust their relative position with respect to the outlet ports. Typically I-SMB units use only four chromatographic columns, and the proponents claim that higher productivity than SMB can be achieved [13].

1.1 Objectives and structure of this thesis

Therefore the objective of this thesis is to analyze and demonstrate I-SMB process and discuss its performance compared to the conventional SMB process in order to explore the potential of this technique in other application fields.

In Chapter 2, I-SMB, one of the modifications of SMB, is presented and analyzed in the frame of the equilibrium theory of chromatography and through detailed simulations. Triangle Theory as developed for the conventional SMB [14, 15] is extended to the I-SMB process design. Additionally, through the equilibrium theory-based cyclic steady-state analysis, the benefits of this process are discussed and it is demonstrated why and how the combination of the synchronous partial feed and partial withdrawal operation implemented in the I-SMB process can indeed improve the separation efficiency as compared to the standard SMB process.

A comparative analysis of the two processes under linear as well as non-linear conditions are presented in Chapter 3 and 4. Experiments are carried out on a properly modified laboratory unit to separate racemic mixtures of the enantiomers of Tröger’s base in ethanol on Chiralpak AD, and simulations are carried out for the same system using the equilibrium dispersive model and a bi-Langmuir isotherm, whose parameters have been preliminarily estimated from pulse and breakthrough
1. Introduction

experiments. The I-SMB separation works successfully even under non-linear conditions, and it has been confirmed that the favorable features of the I-SMB discussed in Chapter 2 are still maintained, i.e., rather simple design criteria for the conventional SMB process, triangle theory, can be extended to the I-SMB, and the I-SMB process can achieve very high product purity with only four columns.

Additionally in Chapter 5 the possibility of an on-line optimizing control of the I-SMB process is studied. It is still common practice to run this type of multi-column continuous process sub-optimally since close to optimal conditions the operation is less robust, and there has been a lot of effort to develop a proper control scheme that exploits full economic potential of standard SMB process [5]. Taking advantage of the existing standard SMB controller [16–18], on-line optimizing control of the I-SMB process is demonstrated through simulations using a virtual I-SMB unit. Finally, concluding remarks are given in Chapter 6.
Chapter 2

I-SMB chromatography: Design criteria and cyclic steady-state*

The I-SMB process is a multi-column chromatographic process, which is a modification of the conventional SMB process, has been applied so far only in the sugar industry and is claimed to achieve higher productivity. In the I-SMB process the time interval between two port switches is divided in two sub-intervals, and only during the first the product streams are collected. The potential of the I-SMB technology is demonstrated in the case of the separation of a binary mixture subject to the linear isotherm by using both the equilibrium theory of chromatography and detailed simulations. It is shown that a I-SMB with only four columns

*The content of this chapter has been published by Katsuo and Mazzotti [19].
can achieve much higher separation performance than a SMB unit with four columns.

2.1 Introduction

The application of SMB chromatography to the separation of enantiomers of chiral compounds is successful because of its excellent performance as compared to column chromatography [8] and of the ease of scaling it, both up and down. Since chiral stationary phases can be relatively expensive compared to others, there has been a continuous effort to find modified SMB schemes that allow for higher productivity or for a smaller number of columns yet guaranteeing the same product specifications [5]. Examples of such modifications are the processes called Varicol, where the ports are switched asynchronously [9], ModiCon, where the feed concentration is modulated during the switch interval [10], PowerFeed, where the feed flow rate is varied [11], and FF-SMB, where the product stream is fractionated for internal re-cycling and re-feeding [12].

In this study, one of such modifications is presented and analyzed in the frame of the equilibrium theory of chromatography and through detailed simulations. This process was invented and patented under the name of improved SMB by Nippon Rensui Corporation, and uses typically only four chromatographic columns [13]. The proponents claim that higher productivity than in the conventional SMB can be achieved, and they have applied it for separations in the sugar industry.

We prefer to call this new process Intermittent Simulated Moving Bed (I-SMB) because this name reflects better its features, as we will see in the
2.2 I-SMB chromatography

Figure 2.1: Scheme of the conventional closed-loop SMB process.

following. In this first part of a series of papers, Triangle Theory as developed for the conventional SMB [14, 15] is extended to the I-SMB process design. Additionally, through the equilibrium theory-based cyclic steady-state analysis, the benefits of this process are discussed and it is demonstrated why and how the combination of the synchronous partial feed and partial withdrawal operation implemented in the I-SMB process can indeed improve the separation efficiency as compared to the standard SMB process. In the next papers of the series experimental evidence of the I-SMB performance under linear and nonlinear conditions will be provided, and results about the I-SMB optimization will be reported.

2.2 I-SMB chromatography

2.2.1 Process description

Fig. 2.1 shows the scheme of the conventional closed-loop SMB process. A series of columns is divided into four zones by two inlet and two outlet ports. The feed solution and the mobile phase are introduced through the inlet ports (feed and desorbent) and the two product streams are withdrawn from the outlet ports (extract and raffinate) continuously. Periodically the port locations are switched in the direction of the fluid
2. I-SMB chromatography: Design criteria and cyclic steady-state

Figure 2.2: Scheme of the I-SMB process and definition of the flow rates. Port switch takes place at the end of step II and at the start of step I.

Flow, thus simulating in a discrete manner a continuous counter-current movement of the stationary phase with respect to the fluid phase.

In the I-SMB process however, as illustrated in Fig. 2.2(a), the time period between two port switches, \( t^* \), is divided into two sub-intervals, namely steps I and II, with duration \( \alpha t^* \) and \( (1 - \alpha) t^* \), respectively. During step I, the unit is operated as a conventional SMB, with two inlets and two outlets, though with zero flow rate in section 4 (Fig. 2.2(b)). During step II all the inlet and outlet ports are closed hence the fluid phase is just circulated along the column train, with identical flow rates in the four sections, thus allowing to move the concentration profiles along the columns and to adjust their relative position with respect to the location of the inlet and outlet ports (Fig. 2.2(c)). Since there is flow in section 4 during step II only, we call the corresponding flow rate \( Q_4 \), and the
three flow rates in sections 1, 2 and 3, which prevail during step I, are called $Q_1$, $Q_2$ and $Q_3$, respectively. Note that only three sections are used during step I in order to reduce the overall length of the unit and to allow for larger flow rates in the columns at the same overall pressure drop, as discussed below. Note also that the choice of having the same flow rate in all sections during step II makes the implementation of the I-SMB mode rather simple.

### 2.2.2 Triangle Theory for I-SMB

For the sake of simplicity, let us consider two components A and B subject to a linear adsorption isotherm:

$$n^*_i = H_i c_i \quad (i = A, B),$$

$$H_A > H_B,$$  \hspace{1cm} (2.1)

where for each component $i$ $H_i$ is its Henry’s constant, whereas $c_i$ is its concentration in the fluid phase and $n^*_i$ is its adsorbed phase concentration in equilibrium with the fluid phase.

Like in the case of the conventional SMB [5, 20], also in the case of the I-SMB under the assumption of infinite column efficiency the constraints to achieve complete separation in sections 2 and 3 and to achieve complete regeneration of the stationary and mobile phase in sections 1 and 4 can be expressed in terms of the residence time of the two components
to be separated in each section of the unit:

Section 1: \[ t_{A,1}^r \leq t^* \]
Section 2: \[ t_{B,2}^r \leq t^* \leq t_{A,2}^r \]
Section 3: \[ t_{B,3}^r \leq t^* \leq t_{A,3}^r \]
Section 4: \[ t^* \leq t_{B,4}^r \]  \hspace{1cm} (2.2)

Taking into account that each I-SMB section experiences two different flow rates during each switch period \( t^* \), the retention time of species \( i \) in the \( j \)-th section \( t_{i,j}^r \) is given by the following equation:

\[
t_{i,j}^r = \frac{V}{\hat{Q}_j} \left[ \epsilon^* + (1 - \epsilon^*)H_i \right] \quad (i = A, B, j = 1, \ldots, 4),
\]  \hspace{1cm} (2.3)

where \( V \) and \( \epsilon^* \) are the column volume and overall void fraction, respectively, whereas \( \hat{Q}_j \) is the flow rate in the \( j \)-th section averaged over one switch period. This is defined as

\[
\begin{align*}
\hat{Q}_j &= \alpha Q_j + (1 - \alpha)Q_4 \quad (j = 1, 2, 3), \\
\hat{Q}_4 &= (1 - \alpha)Q_4.
\end{align*}
\]  \hspace{1cm} (2.4)

It is worth noting that Eq. 2.3 applies also to the conventional SMB when the actual flow rates are used for the average flow rates, i.e. where \( \hat{Q}_j = Q_j \).

Let us introduce the flow rate ratio \( m_j \) defined using the average flow rate, i.e.:

\[
m_j \equiv \frac{\hat{Q}_j t^* - V \epsilon^*}{V(1 - \epsilon^*)} \quad (j = 1, \ldots, 4).
\]  \hspace{1cm} (2.5)

Note that this definition applies also to the conventional SMB when
\( \dot{Q}_j = Q_j \). By using Eq. 2.3, the inequalities on the retention times given by Eq. 2.2 can be readily recast in terms of the flow rate ratios as follows:

\[
\begin{align*}
H_A &\leq m_1, \\
H_B &\leq m_2 \leq H_A, \\
H_B &\leq m_3 \leq H_A, \\
m_4 &\leq H_B.
\end{align*}
\] (2.6)

This demonstrates that at least in the case of linear systems, I-SMB operating conditions can be selected using the same criteria in terms of the flow rate ratios \( m_j \) as those applied in the case of the conventional SMB operation.

Based on the process schemes in Figs. 2.1 and 2.2, it is obvious that the external flow rates can be obtained from the internal flow rates differently for the two units, as given by the following equations:

\[
\begin{align*}
Q_E &= Q_1 - Q_2, \\
Q_F &= Q_3 - Q_2, \\
Q_D &= Q_1 \quad \text{(I-SMB)}, \\
Q_R &= Q_3 \quad \text{(I-SMB)}, \\
Q_D &= Q_1 - Q_4 \quad \text{(SMB)}, \\
Q_R &= Q_3 - Q_4 \quad \text{(SMB)}.
\end{align*}
\] (2.7)

Using these equations and the requirement of non-negativity for both internal and external flow rates yields the following additional con-
2. I-SMB chromatography: Design criteria and cyclic steady-state

Figure 2.3: Complete separation and regeneration region for the I-SMB process. Open symbols represent operating points for the cyclic steady-state analysis. Point P: inside the complete separation region. Point O: at the triangle vertex. Point N: in the region where both product streams are impure. Simulations have been carried out for all operating points connecting points N and P. The values of $m_1$ and $m_4$ are the same for all cases.

Constraints:

$$m_j \geq m_2 \geq m_4 \geq \frac{-e^*}{1 - e^*} \quad (j = 1, 3) \quad \text{(I-SMB)},$$

$$m_j \geq m_k \geq \frac{-e^*}{1 - e^*} \quad (j = 1, 3; k = 2, 4) \quad \text{(SMB)}. \quad (2.8)$$

An example of the complete separation triangle for the I-SMB and the conventional SMB processes is shown in Fig. 2.3.
2.2.3 Minimum switch time design

The I-SMB process has six degrees of freedom, namely the four internal flow rates $Q_j$ ($j = 1, \ldots, 4$), the switch time $t^*$ and the parameter $\alpha$, which defines the duration of sub-interval I relative to the whole switch time $t^*$. To determine the values of these six operating parameters, the constraints on the four $m_j$ values provided above (Eq. 2.6) and two additional constraints need to be enforced.

Typically the chromatographic media, particularly for chiral separations, have a specification on the maximum pressure drop, $\Delta P_{\text{max}}$, i.e., violating this maximum allowable pressure drop would damage the stationary phase and consequently lead to degradation of the separation performance. Therefore, for conventional SMBs, and for I-SMBs as well, the additional constraints to determine the operating conditions require that the total pressure drop in the unit be smaller than or equal to the maximum pressure drop. This is particularly true for highly efficient stationary phases, such as chiral stationary phases, where efficiency limitations are less stringent than pressure drop limitations. Therefore, in the following we assume that pressure drop is the limiting constraint.

The pressure drop $\Delta P_j$ along one column in section $j$ associated to the fluid flow rate $Q_j$ is given by Darcy’s law as:

$$
\frac{\Delta P_j}{L} = \frac{\phi Q_j}{S},
$$

(2.9)

where $L$ and $S$ are the column length and cross-sectional area, respectively, and $\phi$ is a parameter depending on the properties of the packing and of the fluid phase. In the case of multicolumn chromatographic processes, since the flow rates differ in different sections, the total pressure drop $\Delta P$ in the unit must be expressed as the summation of each
section’s pressure drops, i.e.:

\[ \Delta P = \sum_j n_j \Delta P_j \]  

(2.10)

where \( n_j \) is the number of columns in the \( j \)-th section of the unit.

Since the I-SMB experiences two different operating modes during one switch period and the pressure drop constraint applies to both, the following inequalities have to be fulfilled:

\[ \Delta P_I = \sum_{j=1}^{3} n_j \Delta P_j \leq \Delta P_{\text{max}} \quad \text{for sub-interval I}, \]

(2.11)

\[ \Delta P_{\text{II}} = \sum_{j=1}^{4} n_j \Delta P_4 \leq \Delta P_{\text{max}} \quad \text{for sub-interval II}. \]

With a given set of four \( m_j \) values, the condition \( \Delta P_I = \Delta P_{\text{II}} = \Delta P_{\text{max}} \) allows calculating the minimum switch time \( t^* \) and the parameter \( \alpha \), which therefore gives the minimum duration of step I. Using Eqs. 2.5, 2.9 and 2.11, the following relationships are obtained:

\[ t^* = \frac{\phi L^2}{\Delta P_{\text{max}}} \sum_{j=1}^{4} n_j \left( m_j (1 - \epsilon^*) + \epsilon^* \right), \]

(2.12)

\[ \alpha = \frac{\sum_{j=1}^{3} n_j (m_j - m_4) (1 - \epsilon^*)}{\sum_{j=1}^{4} n_j (m_j(1 - \epsilon^*) + \epsilon^*)}. \]

(2.13)

It is worth noting that the expression of the minimum switch time applies also to the conventional SMB operated at the same \( m_j \) values, where only one of the two constraints given by Eq. 2.11 applies. Remarkably, \( t^* \)
and $\alpha$ are independent of each other. For given I-SMB unit and conventional SMB unit having the same geometric configuration, if the same flow rate ratio values and pressure drop constraints are applied when designing the process, the switch time of both processes is the same and the average flow rate in each section of the I-SMB is equal to that of the standard SMB. This implies that the two units achieve the same throughput, i.e. the same amount of feed processed per unit time, when operated at the same feed concentration. Therefore, the I-SMB and the conventional SMB processes can be conveniently compared on the same basis by considering the corresponding flow rate ratios.

### 2.3 Analysis of the cyclic steady-state behavior

We aim at comparing the cyclic steady-state behavior of the conventional SMB process and of the I-SMB process in terms of separation performance. On the one hand we consider for the two techniques operating points sharing the same values of the flow rate ratios, hence, based on the considerations above, the same throughput. On the other hand, the productivity of the process is defined as the amount of product recovered per unit time and per unit volume of the stationary phase (or of the unit) that fulfill the product specifications, typically the average product purities [8]. Therefore, the same throughput in two different units corresponds to the same productivity only if the units have the same total volume, or more specifically the same number of columns of the same size, and if the same product purities are achieved.

Let us consider the graphical representation of the complete separation region defined by Eqs. 2.6 and 2.8 in the $m_2$-$m_3$ plane as shown in Fig. 2.3. For a given value of the flow rate ratios in sections 1 and 4 and for a
fixed value of the switch time \( t^* \), the vertex of the complete separation triangle (point O in the figure) achieves the highest throughput, i.e., the feed flow rate \( Q_F = Q_3 - Q_2 \) is maximized, among the operating points belonging to the complete separation region.

However, the complete separation region has been obtained assuming columns with infinite efficiency. Therefore in the operation of real columns with finite efficiency, due to mass transfer resistance and axial dispersion, and in detailed simulations that account for these effects, the separation does not reach very high product purity in the neighborhood of the triangle’s vertex. This is particularly true for a conventional four column SMB with 1-1-1-1 configuration (one column per section, like in Fig. 2.1). Typically SMB units have in fact six or more columns to overcome this limitation. On the contrary the patent literature claims that a four-column I-SMB unit is not affected by such purity limitations, thus reaching much higher productivity than a conventional SMB [13]. We will address this issue in detail in the following by carrying out a theoretical analysis based on equilibrium theory supported by detailed simulations.

For the sake of simplicity, but without loss of generality, we will consider as a case study the separation of the enantiomers of an allene compound, whose system parameters have been estimated experimentally and are reported in Table 2.1 [21].

2.3.1 Detailed model equations

The models of the I-SMB process and of the conventional SMB process are obtained by combining single column models using proper boundary conditions and implementing proper port switching rules.
2.3 Analysis of the cyclic steady-state behavior

Table 2.1: Column and system parameters [21].

<table>
<thead>
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<th>Column</th>
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<td>$S$ (cm$^2$)</td>
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<tr>
<td>$L$ (cm)</td>
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<tr>
<td>$\epsilon^*$ (-)</td>
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<tr>
<td>$\Delta P_{\text{max}}$ (bar)</td>
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<table>
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<th>System characteristics</th>
<th>Component</th>
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<td>Linear</td>
</tr>
<tr>
<td>$H_i$ (-)</td>
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</tr>
<tr>
<td>$k_{s,i}a_v$ (1/sec)</td>
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</tr>
<tr>
<td>$\epsilon_b D_{ax,i}/u$ (m)</td>
<td>$2.21 \times 10^{-5}$</td>
</tr>
<tr>
<td>$\phi$ (bar min/cm$^2$)</td>
<td>c</td>
</tr>
</tbody>
</table>

- Product of mass transfer coefficient and specific surface.
- Coefficient to determine the dispersion coefficient, where $\epsilon_b$ is bed void fraction and $u$ is superficial velocity.
- Pressure drop coefficient in Eq. 2.9.
The model equations of a chromatographic column described using the so-called equilibrium dispersive model for a binary system subject to a general adsorption isotherm given by \( n_i^* = f_i(c_A, c_B) \) are [22–24]:

\[
\epsilon^* \frac{\partial c_i}{\partial t} + (1 - \epsilon^*) \frac{\partial n_i^*}{\partial t} + u \frac{\partial c_i}{\partial z} = \epsilon^* D_{ap,i} \frac{\partial^2 c_i}{\partial z^2} \quad (i = A,B) . \tag{2.14}
\]

where \( t \) and \( z \) are time and space coordinates, \( u \) is the fluid superficial velocity, and the effects of axial dispersion, proportional to \( D_{ax,i} \), and of the mass-transfer resistance, inversely proportional to \( k_{sv,i} \), are lumped together in an effective dispersion term proportional to the apparent dispersion coefficient \( D_{ap,i} \). The relationship between the actual parameters mentioned above and the apparent dispersion coefficient is given in the case of linear chromatography by the following form of the Van Deemter equation:

\[
HETP_i = \frac{2 \epsilon_b D_i}{u} + \frac{2u}{(1 - \epsilon^*)H_i k_{sv,i}a_v} \left( \frac{(1 - \epsilon^*)H_i}{\epsilon^* + (1 - \epsilon^*)H_i} \right)^2 \tag{2.15}
\]

where \( \epsilon_b \) is the interparticle bed void fraction. The Danckwerts boundary conditions are implemented at the inlet and outlet of each column as:

\[
ed^* D_{ap,i} \frac{\partial c_i}{\partial z} \bigg|_{z=0} = u(c_i|_{z=0} - c_{iIN}) , \quad \frac{\partial c_i}{\partial z} \bigg|_{z=L} = 0 . \tag{2.16}
\]

where \( c_{iIN} \) is the concentration of the inlet stream to the column. For the simulations, the model Eq. 2.14 with the conditions Eq. 2.16 are discretized using a first-order backward difference scheme and the system of ordinary differential equations (ODEs) thus obtained is solved numerically using a ODE solver based on backward differentiation. The model above is regarded as accurate enough to account for all the important
2.3 Analysis of the cyclic steady-state behavior

features of multicolumn chromatographic processes.

2.3.2 Equilibrium theory of chromatography

For the purpose of SMB analysis and design the local equilibrium model of chromatography is effectively used. This is obtained from Eq. 2.14 by setting the apparent dispersion coefficient equal to zero, thus yielding the following equations (one for each species) in the case where the components to be separated are subject to the linear isotherm \( n^*_i = H_i c_i \):

\[
[e^* + (1 - e^*)H_i] \frac{\partial c_i}{\partial t} + u \frac{\partial c_i}{\partial z} = 0.
\]  

(2.17)

Solving the equilibrium theory equations using the method of characteristics demonstrates that, for each species in solution, concentration levels propagate along the column at the concentration independent velocity given by the following equation [25]:

\[
v_i = \frac{u}{e^* + (1 - e^*)H_i}.
\]  

(2.18)

When applied to the different sections of the SMB unit this expression is fully consistent with that of Eq. 2.3 giving the retention time of species \( i \).

2.3.3 Equilibrium theory cyclic steady-state

The cyclic steady-state performance of the conventional SMB and of the I-SMB processes (in a 1-1-1-1 configuration) will be determined using the equilibrium theory model first and then using the detailed model. The three operating points N, O and P in Fig. 2.3 will be considered
Table 2.2: Operating conditions and purity performance of the simulated SMB and I-SMB runs; both units are operated in the 1-1-1-1 configuration; model parameters are reported in Table 2.1; the position of the operating points in the operating parameter plane is shown in Fig. 2.3.

<table>
<thead>
<tr>
<th>Mode</th>
<th>Point</th>
<th>Flow rate ratio ( m_1 )</th>
<th>( m_2 )</th>
<th>( m_3 )</th>
<th>( m_4 )</th>
<th>( t^* ) (sec)</th>
<th>( \alpha )</th>
<th>Flow rate (mL/min) ( Q_1 )</th>
<th>( Q_2 )</th>
<th>( Q_3 )</th>
<th>( Q_4 )</th>
<th>Purity (%)</th>
<th>Raffinate</th>
<th>Extract</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMB</td>
<td>P</td>
<td>3.82</td>
<td>1.96</td>
<td>2.88</td>
<td>1.33</td>
<td>41.1</td>
<td>-</td>
<td>7.43</td>
<td>4.94</td>
<td>6.16</td>
<td>4.08</td>
<td>97.6</td>
<td>99.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>O</td>
<td>3.82</td>
<td>1.66</td>
<td>3.18</td>
<td>1.33</td>
<td>41.1</td>
<td>-</td>
<td>7.43</td>
<td>4.53</td>
<td>6.57</td>
<td>4.08</td>
<td>92.6</td>
<td>96.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>3.82</td>
<td>1.36</td>
<td>3.48</td>
<td>1.33</td>
<td>41.1</td>
<td>-</td>
<td>7.43</td>
<td>4.12</td>
<td>6.98</td>
<td>4.08</td>
<td>84.6</td>
<td>85.5</td>
<td></td>
</tr>
<tr>
<td>I-SMB</td>
<td>P</td>
<td>3.82</td>
<td>1.96</td>
<td>2.88</td>
<td>1.33</td>
<td>41.1</td>
<td>0.28</td>
<td>12.04</td>
<td>3.08</td>
<td>7.49</td>
<td>5.65</td>
<td>99.9</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>O</td>
<td>3.82</td>
<td>1.66</td>
<td>3.18</td>
<td>1.33</td>
<td>41.1</td>
<td>0.28</td>
<td>12.04</td>
<td>1.61</td>
<td>8.96</td>
<td>5.65</td>
<td>96.1</td>
<td>99.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>3.82</td>
<td>1.36</td>
<td>3.48</td>
<td>1.33</td>
<td>41.1</td>
<td>0.28</td>
<td>12.04</td>
<td>0.14</td>
<td>10.43</td>
<td>5.65</td>
<td>84.4</td>
<td>85.8</td>
<td></td>
</tr>
</tbody>
</table>
for the equilibrium theory analysis, the first and the third being outside and inside the complete separation region, respectively, and the second being on its vertex. The operating parameters in sections 1 and 4 are the same for all operating points, as shown in Fig. 2.3 and reported in Table 2.2 where together with the flow rate ratios also the switch time, step ratio, flow rates and product purities (as calculated through detailed simulations, as discussed below) are reported.

**Conventional SMB**

Let us consider Fig. 2.4(b), which refers to the conventional SMB operation at the operating point O, i.e. at the vertex of the complete separation region in the $m_2$-$m_3$ plane. This is a space-time diagram representing the SMB cyclic steady-state behavior, where the fluid flow is from left to right. The four SMB columns (numbered from left to right) are considered during the time interval $t^*$; the inlet and outlet ports are indicated underneath the horizontal axis, and will be shifted by one column to the right at the end of the switching period.

The solid and the dashed lines represent the trailing (tail) and the leading (front) edges of the more and less retained component, respectively, and delimit the area in the physical plane where the relevant component is present. Between B’s trailing edge and A’s leading edge both components are present. Thus, the position of the leading edge of component A indicates that there is no A in column 3 at the beginning of the time interval; that it enters column 3 because it is in the feed and in the outlet of column 2; and that component A reaches the end of column 3 (corresponding to the raffinate port) exactly at the end of the time interval, when upon port switch the leading edge of A finds itself again at the beginning of the new column 3, thus avoiding raffinate pollution.
Figure 2.4: Equilibrium theory cyclic steady-state solutions of conventional 4-column SMB and I-SMB processes. (a) Conventional SMB, point P. (b) Conventional SMB, point O. (c) Conventional SMB, point N. (d) I-SMB, point P. (e) I-SMB, point O. (f) I-SMB, point N.

by A. Likewise, since the trailing edge of B remains in column 2 and does not reach column 1, there is no extract pollution by B. The slopes of the A and B fronts are the reciprocal of their propagation velocity as given by Eq. 2.18 and calculated using the column superficial velocity, i.e. $Q_j/S$, hence they differ for A and B and from column to column. Cyclic steady-state is attained when the species profile at the end of the time interval is the same as the profile at the beginning, but shifted by one column to the right. This requirement is fulfilled by the diagram in Fig. 2.4(b) (as well as by the other five diagrams in the same figure).

From Eqs. 2.2, the position of A’s leading front in column 3 and of B’s trailing front in column 2 implies that $t_{A,3}^r = t^*$ and that $t_{B,2}^r = t^*$, re-
2.3 Analysis of the cyclic steady-state behavior

respectively. From Eqs. 2.6 applied to the conventional SMB, these are equivalent to \( m_3 = H_A \) and \( m_2 = H_B \), i.e. the vertex of the complete separation region in Fig. 2.3. These equalities are replaced by inequalities in the other two columns, since flow rates are such that A is faster and B is slower in columns 1 and 4, respectively, i.e. \( t_{rA,1}^* < t^* \) and \( t_{rB,4}^* > t^* \), and \( m_1 > H_A \) and \( m_4 < H_B \). As a consequence, component A is completely eluted from column 1 at the end of the time interval illustrated in Fig. 2.4(b), whereas component B is absent from column 4 at the beginning of the time interval.

Let us now consider Fig. 2.4(a) that refers to the operating point P within the complete separation region. It is apparent that \( t_{rA,3}^* > t^* \) and that \( t_{rB,2}^* < t^* \), and thus also in this case extract and raffinate are not polluted. However, there is a certain clearing, i.e. separation, (in space) between the position reached by the leading front of A at the end of the time period between two port switches and the raffinate port, which is missing in the case of Fig. 2.4(b). In the latter case, any deviation from the equilibrium theory prediction, e.g. due to axial dispersion, causes pollution of the raffinate. The same situation occurs for component B, whose trailing edge in Fig. 2.4(a) reaches the end of column 2 earlier than when ports are switched and the extract port is moved to the end of column 2 (clearing in time, measured on the vertical axis at the position of the feed port), whereas in Fig. 2.4(b) any deviation from ideality would cause extract pollution.

Finally, Fig. 2.4(c) refers to the operating point N outside the complete separation region. Since \( t_{rA,3}^* < t^* \) and \( t_{rB,2}^* > t^* \), the cyclic steady-state shows that both extract and raffinate are polluted.
I-SMB

Figs. 2.4(d), (e) and (f) refer to the I-SMB operation at points P, O and N in the $m_2$-$m_3$ plane. In the first sub-interval (step I) the slope of the fronts differ for the two components in the same column because of the different Henry’s constants, and for the same component in different columns because of the different flow rates. Fronts do not propagate into column 4, because there is no flow in that column during step I. In the second sub-interval (step II), fronts of the same species have the same slope in all columns because the flow rate is the same along the I-SMB unit in step II.

Let us now consider Fig. 2.4(e), which refers to the operation at the vertex of the complete separation region. As in Fig. 2.4(b), A’s leading edge connects the feed port at the beginning of the time interval to the raffinate port at its end, which is the phenomenological manifestation of the optimal condition $m_3 = H_A$. However, A’s leading edge is made of two segments of different slopes, and the clearing in space between it and the raffinate port is the one observed at the end of step I, as no raffinate is withdrawn during step II. Such clearing is much larger than that observed in the case of the conventional SMB operated at point P (see Fig. 2.4(a)), i.e. well within the complete separation region. B’s trailing edge occupies a small portion of column 2 during step I and a large portion of column 3 during step II. As a consequence, the clearing in time between B’s trailing edge and the position where the extract port is moved at the end of step II is very large, corresponding to more than half of $t^*$. Overall, A’s leading edge and B’s trailing edge are very close, i.e. much closer than in the SMB operation under the same conditions (Fig. 2.4(b)).

This is the key result of our analysis. At the vertex of the complete
2.3 Analysis of the cyclic steady-state behavior

Figure 2.5: Product purities for the conventional SMB and the I-SMB processes calculated using the equilibrium dispersive model for the operating points on the segment connecting points N and P in Fig. 2.3: (a) raffinate; (b) extract.

In the separation region the positions of the components’ fronts in the I-SMB are such that, contrary to the case of the conventional SMB process, the effect of any small deviation from the ideal equilibrium theory behavior, due to axial dispersion or mass transfer resistance, can be tolerated by the unit without spoiling the products’ purities.

This effect is also evident in the case of the operating point P, within the complete separation region, as illustrated in Fig. 2.4(d). Under the operating conditions of point N, outside the complete separation region, B’s trailing edge and A’s leading edge are moved backwards toward column 2 and forward toward column 4, respectively, as shown in Fig. 2.4(f). Considering that products are collected only during step I, it can be readily seen that the degree of products’ pollution in Figs. 2.4(c) and (f) is very similar.
2.3.4 Detailed simulations of the cyclic-steady state

All results obtained using equilibrium theory in Section 2.3.3 are confirmed by analyzing the SMB and I-SMB cyclic steady-state using the equilibrium dispersive model defined in Section 2.3.1. The product purities calculated for a number of operating points along the segment in the $m_2 - m_3$ plane connecting the operating points N, O and P in Fig. 2.3 are plotted as a function of a coordinate along the segment, namely $m_2$, in Fig. 2.5. The same purities in the operating points N, O and P are reported in Table 2.2. Note that the same values of $t^*$ and $\alpha$ apply for all points along the N to P segment. It can be readily observed that the product purities drop as $m_2$ decreases in the case of the conventional SMB earlier than in the case of the I-SMB. More specifically in the case of I-SMB point P achieves indeed complete separation, whereas point O, i.e. the theoretical optimal point, exhibits very high extract purity and rather high raffinate purity. As predicted, SMB purity performance is much worse in point O, and not as good in point P, although this should be in the complete separation region. Interestingly, and again as predicted, product purity is the same for SMB and I-SMB operated outside the complete separation region, i.e. point N. This result demonstrates that the I-SMB process achieves higher productivity than the conventional SMB, because for a given purity specification the I-SMB can be operated closer to the tip of the triangle than the SMB, hence the feed flow rate and the productivity can be larger accordingly.

Detailed simulations allow also analyzing the calculated concentration profiles in the fluid phase. These are shown in Figs. 2.6 and 2.7 for SMB and I-SMB operation, respectively, at point P, i.e. within the complete separation region. The cyclic steady diagrams of Figs. 2.4(a) and (d) are shown in the middle of the two figures; underneath them there are
2.3 Analysis of the cyclic steady-state behavior

Figure 2.6: Conventional SMB operation at operating point P. (a) Steady-state fluid phase concentration profile at the end of the switch. (b) Equilibrium theory cyclic steady-state solution. (c) Steady-state fluid phase concentration profile at the beginning of the switch. Mobile phase concentration profiles are calculated for a total feed concentration of 0.05 g/L.
Figure 2.7: I-SMB operation at operating point P. (a) Steady-state fluid phase concentration profile at the end of the switch. (b) Equilibrium theory cyclic steady-state solution. (c) Steady-state fluid phase concentration profile at the beginning of the switch. Mobile phase concentration profiles are calculated for a total feed concentration of 0.05 g/L.
the concentration profiles at the beginning of the time interval, whereas above them there are those at the end of the switch time interval for the SMB and at the end of step I for the I-SMB, i.e. at the point in time where instantaneous product pollution is expected to be the most intense. It can readily be observed that in the conventional SMB case both the raffinate and the extract are polluted, albeit the latter only slightly. On the contrary, in the I-SMB case there is no such pollution and the feed mixture is indeed separated completely.

Detailed simulations confirm also that B’s trailing edge and A’s leading edge are much closer in the I-SMB unit of Figure 2.7 than in the conventional SMB unit of Figure 2.6, as predicted.

### 2.3.5 Conclusions

This paper presents the intermittent SMB technology, analyzes for the first time its behavior, and demonstrates why and how it has the potential to outperform the conventional SMB process. Such proof is based on the equilibrium theory of chromatography and is supported by detailed simulations. The impact of partial feed and withdrawal operations on the SMB performance has been discussed in previous publications [26–28]. Nevertheless, we believe that the I-SMB technology is simpler to implement, from both a theoretical and a practical point of view, and more effective. We are planning to substantiate this statement with future work that addresses systems subject to nonlinear adsorption isotherms and I-SMB optimization, as well as the experimental validation of all the theoretical results. We believe that the deployment of the I-SMB technology for difficult separations, such as that of the enantiomers of a chiral compound in the case of low selectivity, can be a major breakthrough in preparative multi-column chromatography.
2. I-SMB chromatography: Design criteria and cyclic steady-state

Nomenclature

- \( c_i \): fluid phase concentration of component \( i \)
- \( D_i \): axial dispersion coefficient of component \( i \)
- \( H_i \): Henry’s constant of component \( i \)
- \( k_{s,i}a_v \): mass transfer coefficient of component \( i \)
- \( L \): column length
- \( m_j \): flow rate ratio in section \( j \) of I-SMB and conventional SMB
- \( n_i^* \): adsorbed phase concentration of component \( i \) in equilibrium with the mobile phase
- \( n_j \): number of the columns in section \( j \)
- \( \Delta P_j \): pressure drop in section \( j \)
- \( Q_j \): volumetric flow rate in section \( j \)
- \( \hat{Q}_j \): average volumetric flow rate in section \( j \)
- \( Q_P \): volumetric flow rate at port \( P \)
- \( S \): cross-sectional area of the column
- \( t \): time coordinate
- \( t^* \): switch time
- \( t_{i,j}^r \): retention time of component \( i \) in section \( j \)
- \( u \): superficial velocity
- \( v_i \): propagation velocity of component \( i \)
- \( V \): column volume
- \( z \): axial coordinate along the column

Greek letters

- \( \alpha \): step ratio of I-SMB
- \( \epsilon^* \): overall bed void fraction
- \( \epsilon_b \): inter-particle void fraction
2.3 Analysis of the cyclic steady-state behavior

\( \phi \) pressure drop coefficient in Eq. 2.9

**Subscripts and superscripts**

- A: component A
- B: component B
- \( i \): component index
- \( j \): section index
2. I-SMB chromatography: Design criteria and cyclic steady-state
Chapter 3

I-SMB chromatography: Separation of Tröger’s base enantiomers*

The I-SMB process is a modification of the conventional SMB process that has been analyzed theoretically in Chapter 2 [19]. Here, we present a comparative analysis of the two processes, each operated in a six-column 1-2-2-1 configuration (one column in sections 1 and 4 and two columns in sections 2 and 3) and in a four-column 1-1-1-1 configuration. Experiments are carried out on a properly modified laboratory unit to separate racemic mixtures of the enantiomers of Tröger’s base in ethanol on Chiralpak AD at a total feed concentration of 1 g/L. Simulations are carried out for the same system using the equilibrium dispersive model

*The content of this chapter has been published by Katsuo and Mazzotti [29].
and a bi-Langmuir isotherm, whose parameters have been preliminarily estimated from pulse and breakthrough experiments. Experiments and simulations are fully consistent and demonstrate that the four-column I-SMB process (but not the four-column SMB process) can separate the two enantiomers at very high purity and achieve a productivity twice as large as that of the six-column I-SMB and conventional SMB processes with the same solvent consumption.

3.1 Introduction

I-SMB chromatography identifies a modification of the conventional SMB process, which has been patented by the Nippon Rensui Corporation [13] and has been analyzed theoretically in Chapter 2 [19].

In a conventional four-section SMB unit the feed and the mobile phase (desorbent) are introduced between sections 2 and 3 and between sections 4 and 1, respectively, whereas the extract (containing the more retained species, indicated with A in the following) is collected between sections 1 and 2 and the raffinate (containing the less retained component B) is withdrawn between sections 3 and 4. The outlet of section 4 is recycled to section 1, and the continuous countercurrent movement of the adsorbent is simulated by periodically switching the inlets and outlets in the direction of the fluid flow; the time interval between two switches is the switch time, i.e. \( t^* \).

In the I-SMB process the switch time \( t^* \) is divided into two sub-intervals, i.e. step I of duration \( at^* \) and step II of duration \( (1 - a)t^* \). In the first the unit is operated as a conventional SMB, with two inlets and two outlets but no flow through section 4; the whole flow through section 3 is collected in the raffinate stream. In the second sub-interval, the
inlet and outlet ports are closed and the fluid is just circulated along the I-SMB’s four sections, thus moving the concentration profiles along the columns and adjusting their relative position with respect to inlet and outlet ports [19].

In the SMB process and in its modifications, under optimal operating conditions and for each product stream the polluting component reaches the outlet port at the end of the time interval just before the ports are switched [5]. This implies that in general the optimal operating conditions are also the least robust, because any deviations from the predicted behavior, which can be induced by uncertainties regarding the system such as adsorption isotherm and column inefficiencies, by disturbances in keeping the fixed operating conditions, i.e. flow rates and temperature, and by aging, easily lead to degradation of the product purity. This is not the case in the I-SMB process where, due to the intermittent feed and product withdrawal, the polluting species reaches the product outlet at a certain finite time after the corresponding port has been shut off. As a consequence, it is possible to demonstrate using both the equilibrium theory of chromatography and detailed simulations that an I-SMB unit with only four columns can achieve very high purity performance, which is not accessible to a conventional SMB unit with the same four columns [19].

So far the I-SMB technology has been applied to separations in the sugar industry only. The aim of this work is to extend it to chiral chromatography [5] and to demonstrate its potential through experiments, supported by detailed simulations. After showing how to implement the I-SMB operation in an existing laboratory SMB unit and after characterizing the adsorption isotherms of the enantiomers of the Tröger’s base (on a Chiralpak AD column using ethanol as mobile phase), a set of experimental results will be presented and discussed to analyze and compare the
separation performance of four-column (1-1-1-1 configuration, i.e. one column in each section) and six-column (1-2-2-1 configuration, i.e. two columns in sections 2 and 3) I-SMB and conventional SMB operations. The experimental data will be evaluated in light of the corresponding simulation results, obtained using a detailed model.

3.2 Practicalities

3.2.1 Implementation of the I-SMB technology

Fig. 3.1 shows one of the possible technical implementations of the I-SMB process. The scheme is similar to that of a conventional SMB unit, the only difference being that the Raffinate pump used in a conventional SMB is replaced by a simple on-off valve. In the figure the unit has four columns arranged in a 1-1-1-1 configuration; a six-column 1-2-2-1 unit would simply have two columns between extract and feed ports and between feed and raffinate. For the sake of clarity the scheme is simplified, namely for each inlet and outlet manifold, for instance the feed port, only the connection to the column that is active in the current configuration is shown, i.e. to column 3 in the case of the feed, whereas those to the other columns are not shown. The dashed line from section 4 and into section 1 represents the physical connection between successive columns, which is not active for the column in section 4.

During step I, the feed and desorbent are introduced and the extract is withdrawn through the corresponding pumps in Fig. 3.1. At the same time, the raffinate on-off valve is open so as to withdraw as raffinate product the whole stream from section 3, thus letting no flow through section 4.
Figure 3.1: Scheme of the laboratory multicoloumn chromatography unit. The displayed configuration is the one needed to implement the I-SMB mode; in case of the conventional SMB process the on-off valve at the raffinate port is replaced by a pump, such as the one at the extract port.
To switch the operation to the circulation mode of step II, the on-off valve at the raffinate port is shut off, and so are the feed and extract pumps. At the same time the desorbent pump before section 1 continues operation at the selected flow rate corresponding to the circulation flow through the unit.

### 3.2.2 SMB/I-SMB experimental set-up

The laboratory unit is based on a modified ÄKTA™ Explorer 100 system (GE Healthcare) and its configuration is consistent with the scheme of Fig. 3.1 (where each section can consist of one or more columns). All its components, i.e. multiposition valves, pumps, and detectors, are controlled by the UNICORN™ software (GE Healthcare) [21, 30].

In a small scale laboratory SMB unit, the extra-column dead volume has a big impact and has to be properly accounted for in choosing the operating conditions [20, 21]. Such dead volume consists of the parts connecting two consecutive chromatographic columns, which have been determined very precisely using a tracer: namely from the column to the outlet manifold, of volume $V_b = 0.02 \text{ mL}$; from the outlet manifold to the inlet manifold before the next column, including the check valve (of overall volume $V_c = 0.18 \text{ mL}$); from the outlet manifold to the inlet of the next column, of volume $V_a = 0.03 \text{ mL}$.

The similarity between the I-SMB and the conventional SMB process together with the flexibility of the hardware and software described above allow carrying out the separation of interest in both operating modes with minimal equipment modifications.
3.2 Practicalities

3.2.3 Materials

This work studies the separation of the enantiomers of the Tröger’s base, \((\pm)-2,8\text{-dimethyl-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine}\). This compound has often been used in chiral chromatography studies [31–36]. According to the thermodynamic model developed for the solid-liquid equilibrium of Tröger’s base enantiomers in ethanol, the solubility of the racemate at room temperature is estimated to be around 18 g/L [37].

The racemic mixture of Tröger’s base was purchased from Sigma-Aldrich, and purified before use by recrystallization from ethanol (Merck, Scharlau). Chiralpak AD (Chiral Technologies Europe) was used as chiral stationary phase and ethanol as mobile phase. Analytical chromatography was performed on a Agilent LC System 1100 Series using the same stationary phase. All chromatographic columns had a 0.46 cm diameter and were prepacked. The SMB columns were 15 cm long, whereas the analytical column was 25 cm long. The overall void fraction, \(\epsilon^*\), of each column was determined by injecting 1,3,5-tris-tert-butylbenzene (TTBB) from Fluka, which is considered to be non-retained, according to the following equation:

\[
\epsilon^* = \frac{t_0 Q}{V},
\]

where \(V\) is the column volume, \(Q\) is the applied flow rate, and \(t_0\) is the residence time of a non-retained species (see Table 3.1). The extra-column dead volume of the analytical set-up has been properly accounted for in all measurements. All experiments were carried out at \(T = 23 \pm 1^\circ C\).

The pressure drop \(\Delta P_j\) along a column in section \(j\), subject to a fluid
flow rate $Q_j$ has been shown to be given by Darcy’s law, i.e.:

$$\frac{\Delta P_j}{L} = \frac{\phi Q_j}{S},$$  \hspace{1cm} (3.2)  

where $L$ and $S$ are the column length and cross-section, respectively, and the proportionality constant $\phi$ depends on the column packing and on the fluid phase properties. Its value has been measured and is reported in Table 3.1.

### 3.3 Preliminaries

#### 3.3.1 Mathematical model

The conventional SMB and the I-SMB processes are described using a column model for each column of the multicolumn unit; these model equations are then combined through proper overall and component material balances at the nodes between columns and the port switching mechanism is properly implemented (with due differences for the two operating modes). Each column model consists of the classical equilibrium dispersive model [22–24]. All the details about the model equations and their implementation in the context of this study are not repeated here as they have been discussed in Chapter 2 [19]. The relevant model parameters have been measured as presented in the next section and are reported in Table 3.1.
Table 3.1: Column and system parameters.

<table>
<thead>
<tr>
<th>Column</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>$S$ (cm²)</td>
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<td></td>
</tr>
<tr>
<td>$L$ (cm)</td>
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<td></td>
</tr>
<tr>
<td>$\epsilon^*$ (-)</td>
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<td></td>
</tr>
<tr>
<td>$\Delta P_{\text{max}}$ (bar)</td>
<td>40</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>System characteristics</th>
<th>Component A</th>
<th>Component B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isotherm</td>
<td></td>
<td>Bi-Langmuir</td>
</tr>
<tr>
<td>$a_{i,1}$ (-)</td>
<td>3.99</td>
<td>1.56</td>
</tr>
<tr>
<td>$b_{i,1}$ (L/g)</td>
<td>0.0107</td>
<td>0.0132</td>
</tr>
<tr>
<td>$a_{i,2}$ (-)</td>
<td>0.986</td>
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</tr>
<tr>
<td>$b_{i,2}$ (L/g)</td>
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<td>0.136</td>
</tr>
<tr>
<td>$k_{s,i}a_v$ (1/sec)</td>
<td>1.81</td>
<td>2.96</td>
</tr>
<tr>
<td>$\epsilon_b D_i / u$ (m)</td>
<td></td>
<td>3.01 x 10^{-4}</td>
</tr>
<tr>
<td>$\phi$ (bar min/cm²) d</td>
<td></td>
<td>0.1</td>
</tr>
</tbody>
</table>

a Maximum allowable pressure drop of the column.
b Product of mass transfer coefficient and specific surface.
c Coefficient to determine the dispersion coefficient, where $\epsilon_b$ is bed void fraction and $u$ is superficial velocity.
d Pressure drop coefficient in Darcy’s low, $\Delta P/L = \phi u$. 
3.3.2 Adsorption isotherms

The competitive adsorption isotherms of the Tröger’s base enantiomers in ethanol on Chiralpak AD at 23°C have been determined through diluted pulse injections in the 25 cm column (linear retention behavior), overloaded pulse injections in the same column (nonlinear retention behavior), and frontal analysis breakthrough experiments in the 15 cm column, in all cases using racemic solutions of different concentrations up to the solubility limit. All experiments are consistent in indicating that both enantiomers are subject to a favorable adsorption isotherm. This is different from but not inconsistent with what observed in the past for the same enantiomers on different stationary phases, where rather complicated behavior was observed [31, 32, 34–36]. However, it is not possible to describe the observed pulse, breakthrough and elution profiles using a simple Langmuir isotherm, and a bi-Langmuir isotherm, as given by the following equation, has been necessary:

\[
n_i^* = \frac{a_{i,1} c_i}{1 + \sum_j b_{j,1} c_j} + \frac{a_{i,2} c_i}{1 + \sum_j b_{j,2} c_j} \quad (i = A, B),
\]

\[
H_A = a_{A,1} + a_{A,2} > a_{B,1} + a_{B,2} = H_B.
\]

The parameters of the equation above have been estimated by applying the inverse method [38], i.e. by fitting, using the equilibrium dispersive model mentioned above, the measured profiles; such method allows to obtain at the same time the axial dispersion coefficients as well. All model parameters are given in Table 3.1.

In Fig. 3.2 the measured elution profiles of three frontal analysis experiments at a total feed concentration \( c_T^* = 12.1, 15.0, \) and 18.0 g/L, together with the simulations carried out using the estimated parameters, are
shown. Using the bi-Langmuir isotherm one can successfully reproduce through simulations (solid and dashed lines) the experimental profiles as obtained through HPLC analysis of the fractions collected during elution (symbols).

Fig. 3.3 shows the adsorption isotherms, where the symbols are experimental data calculated from the mass balances applied to the breakthrough profiles of the frontal analysis experiments, and the curves are calculated using Eq. 3.3. Fig. 3.3(a) shows the pure component isotherm of component B, i.e. where \( c_A = 0 \), whereas Fig. 3.3(b) plots the adsorbed phase concentration of A and B in contact with a racemic solution, i.e. where \( c_A = c_B \). By comparing the expression of the bi-Langmuir isotherm, Eq. 3.3, with the values of the parameters in Table 3.1, it can be observed that the first part of the isotherm (the first term in the right-
3. I-SMB chromatography: Separation of Tröger’s base enantiomers

![Graph of Bi-Langmuir adsorption isotherms](image)

Figure 3.3: Bi-Langmuir adsorption isotherms. Solid line: component A, dashed line: component B. Symbols are values computed from the mass balance calculation of breakthrough experiments; (□) component A; (○) component B. (a) Pure component B adsorption isotherm, i.e. where Eq. 3.3 with \(c_A = 0\). (b) Competitive adsorption isotherms for equilibrium of the stationary phase with racemic mixtures, i.e. Eq. 3.3 with \(c_A = c_B\).

Hand side of Eq. 3.3) has a much higher capacity than the second, as expressed by the ratio \(a_{i,1}/b_{i,1}\) and \(a_{i,2}/b_{i,2}\), respectively, which is of the order of 100 in the first part as compared to about 2 in the second for both components A and B. On the other hand the first part is much less nonlinear, because \(b_{i,1}c_j\) is about 1 when \(c_j \approx 100\) g/L whereas \(b_{i,2}c_j\) is about 1 when \(c_j\) is only about 2 g/L, i.e. at a much lower concentration. The selectivity of the two terms is on the contrary similar, i.e. between 2.5 and 3.5.

### 3.3.3 Separation performance indicators

The separation performance of the conventional SMB and of the I-SMB processes can be compared based on a number of performance indica-
3.3 Preliminaries

tors. Their definition is based on the average concentration of A and B in extract and raffinate, which is defined as follows:

$$\bar{c}_{P,i} = \frac{1}{\alpha t^*} \int_{Nt^*}^{(N+\alpha)t^*} c_{P,i} \, dt,$$

(3.4)

where the average is calculated on a period of time equal to the switch time, $t^*$. The index $i$ equals A or B; the index P identifies the product stream, i.e. either extract or raffinate, and the step ratio $\alpha$ is defined as above for the I-SMB process and is equal to 1 for a conventional SMB.

The product purities $X_i$ is defined as:

$$X_A = \frac{\bar{c}_{E,A}}{\bar{c}_{E,A} + \bar{c}_{E,B}} , \quad X_B = \frac{\bar{c}_{R,B}}{\bar{c}_{R,A} + \bar{c}_{R,B}} ,$$

(3.5)

whereas the recovery of each component is given by:

$$Y_A = \frac{Q_E \bar{c}_{E,A}}{Q_{FCF,E}} , \quad Y_B = \frac{Q_R \bar{c}_{R,B}}{Q_{FCF,B}} ,$$

(3.6)

where $Q$ is a flow rate, and the subscript refers to the relevant external stream, namely extract, raffinate, feed or desorbent. Through the overall mass balance, the following relationships between purity and recovery can be derived:

$$Y_A = \frac{(2X_B - 1)X_A}{X_A + X_B - 1} , \quad Y_B = \frac{(2X_A - 1)X_B}{X_A + X_B - 1} .$$

(3.7)

Therefore, in the case of very high purity for both products also their recovery is obviously very large.

The productivity, $Pr$, which is very important from an economical point of view, is defined as the total amount of recovered products per unit
volume of the stationary phases per unit time, i.e.:

\[ Pr = \frac{\alpha (Q_{E}c_{E,A} + Q_{R}c_{R,B})}{\sum n_{j}V}, \]  

(3.8)

where also in this case \( \alpha \) must be taken as 1 in the conventional SMB; in the denominator \( n_{j} \) is the number of columns in section \( j \). Finally, the specific solvent consumption per unit amount of the recovered products (made dimensionless by multiplying the solvent flow rate by the total feed concentration) is given by:

\[ SC = \frac{(Q_{D} + Q_{F})(c_{F,A} + c_{F,B})}{Q_{F}(Y_{A}c_{F,A} + Y_{B}c_{F,B})}. \]  

(3.9)

### 3.4 Results

In this section, first the criteria applied to select the operating conditions for I-SMB and conventional SMB are spelled out. Then, a rather comprehensive series of simulations will highlight important features of the performance of the two alternative processes in different configurations. Finally, a set of experiments will allow assessing the performance of I-SMB as compared to SMB in the laboratory unit described above. It is worth noting that all experiments, simulations and calculations in this work have been carried out for a rather low total feed concentration, namely \( c_{F}^{T} = 1.0 \) g/L. This is a rather low concentration, corresponding supposedly to a retention behavior very close to linear.
3.4 Results

3.4.1 Design through triangle theory

In Chapter 2 [19], it has been shown that under linear conditions the triangle theory for the design of conventional SMB processes can be extended to the I-SMB operation. Such approach defines criteria for the choice of the flow rate ratios to achieve - under ideal conditions - complete separation. The flow rate ratio in section \( j \), \( m_j \), is defined as:

\[
m_j \equiv \frac{\hat{Q}_j t^* - Ve^*}{V(1 - e^*)} \quad (j = 1, ..., 4),
\]

where \( \hat{Q}_j \) is the average flow rate in section \( j \). The latter coincides with the sectional flow rate in the case of the conventional SMB unit, but has to be calculated accounting for the two parts of the switch period in the I-SMB case as follows:

\[
\begin{align*}
\hat{Q}_j &= \alpha Q_j + (1 - \alpha)Q_4 \quad (j = 1, 2, 3), \\
\hat{Q}_4 &= (1 - \alpha)Q_4,
\end{align*}
\]

where \( Q_1 \), \( Q_2 \) and \( Q_3 \) are the flow rates in the corresponding sections during sub-interval I of the switch period, whereas \( Q_4 \) is the flow rate common to all sections during sub-interval II. In the case of a system subject to linear isotherms, the average flow rate ratios have to fulfill the well known explicit criteria obtained through the so-called triangle theory, namely \( m_1 \geq H_A \geq m_3 \geq m_2 \geq H_B \geq m_4 \geq -e^*/(1 - e^*) \), where \( H_A \) and \( H_B \) are the Henry’s constants of the two species to be separated [19].

It is worth noting that in the case of a system subject to the bi-Langmuir isotherm of Eq. 3.3 the linear design criteria above apply only at infinite dilution. A feed concentration of 1 g/L as applied in this study is large enough to call for the application of the nonlinear criteria, which in
Figure 3.4: Triangle theory complete separation region for the separation of the Tröger’s base enantiomers at 1 g/L total feed concentration calculated for the bi-Langmuir isotherm. The upper bound for $m_4$ is calculated for the $m_2$ and $m_3$ values corresponding to the tip of the complete separation region. The rectangular region and the symbol (○) identify all the combinations of average flow rate ratio values where simulations have been carried out.

the case of the bi-Langmuir isotherm and for a conventional SMB have been derived in detail elsewhere [39]. Such criteria can be represented graphically in the space of the flow rate ratios as shown in Fig. 3.4. Note that the actual boundary on $m_4$ depends on the values of $m_2$ and $m_3$ chosen for the specific operation, but that for the sake of simplicity the boundary shown in the diagram corresponds to the $m_2$ and $m_3$ values of the vertex of the complete separation region. No exact criteria for nonlinear I-SMB separations have been derived so far. Considering the rather low feed concentration, which is reflected by the fact that the calculated triangle shaped complete separation region shown in Fig. 3.4 is not very different from the right triangle with the same base points.
on the diagonal that one would obtain for a linear separation with the same Henry’s constants, we assume that the same criteria apply for both conventional SMB and I-SMB. This conjecture will be challenged below through detailed simulations.

The operation of a conventional SMB requires that the four internal flow rates, i.e. \( Q_j \), and the switch time, \( t^* \), are defined, whereas that of a I-SMB unit involves the additional parameter \( \alpha \). Four conditions on these parameters are provided by choosing the values of the four average flow rate ratios, i.e. dimensionless parameters, that fulfill the constraints above. The others are selected by accounting for the actual velocities in the columns that control column efficiency and pressure drop. Which of the two is limiting depends on the nature of the stationary phase. In the case of chiral separations using highly efficient chiral stationary phases it is normally the pressure drop that is limiting. In this case, by enforcing the condition that the pressure drop through the set of columns be always equal to its maximum permitted value, i.e. \( \Delta P_{\text{max}} \), the following equation for \( t^* \) (for both SMB and I-SMB) and \( \alpha \) (for I-SMB only) are obtained [19]:

\[
\begin{align*}
    t^* &= \frac{\phi L^2}{\Delta P_{\text{max}}} \sum_{j=1}^{4} n_j \left( m_j(1 - e^*) + e^* \right), \\
    \alpha &= \sum_{j=1}^{3} \frac{n_j (m_j - m_4) (1 - e^*)}{\sum_{j=1}^{4} n_j \left( m_j(1 - e^*) + e^* \right)}. 
\end{align*}
\]

These equations are based on the assumption that pressure drop follows Darcy’s law, i.e. Eq. 3.2. This is the so-called minimum switch time design, and will be applied for all simulations in this work.
3.4.2 Extra-column dead volume in the I-SMB unit

In the case of experiments, rules are needed to take into account the effect of the extra-column dead volume, which is important in the case of small laboratory units where the volume of tubings and connections is not negligible when compared with the column volume. In the case of the I-SMB process, the same concepts have to be applied as for the conventional SMB unit, as described in previous papers [20, 21].

The dead volume in the \(j\)-th section of a multicolumn chromatographic unit can be divided in two parts, i.e. \(V_{j,u}^{D}\) and \(V_{j,d}^{D}\), which are located upstream and downstream of the column, respectively. In a conventional SMB the fluid phase flows through these volumes, as well as through the column, at the flow rate \(Q_j\). In an I-SMB unit, we assume that the upstream dead volume is flown through at the flow rate \(Q_j\), i.e. during step I (0 for section 4), and the downstream volume at the flow rate \(Q_4\), i.e. during step II. Therefore, the volumes covered by species \(i\) during steps I and II are calculated as:

\[
V_{i}^{I} = V_{j}^{D,u} + \frac{\alpha t^* Q_j - V_{j}^{D,u}}{e^* + (1-e^*)H_i},
\]

\[
V_{i}^{II} = V_{j}^{D,d} + \frac{(1 - \alpha) t^* Q_4 - V_{j}^{D,d}}{e^* + (1-e^*)H_i}.
\]

The design constraint is that the sum of these two volumes equal the sum of the column volume and of the overall extra-column dead volume, i.e. \(V_{i}^{I} + V_{i}^{II} = V + V_{j}^{D}\), where \(V_{j}^{D}\) is the total external-column dead volume in section \(j\), i.e. \(V_{j}^{D} = V_{j}^{D,u} + V_{j}^{D,d}\). Using Eqs. 3.11 and 3.14 yields the
following relationship:

\[\dot{Q}_j - \frac{V_j^D}{t^*} = \frac{V [\epsilon^* + (1 - \epsilon^*)H_i]}{t^*},\]  
(3.15)

which is easy to be shown applicable also to the conventional SMB when the average flow rates are taken as the constant flow rates in the SMB unit.

The left-hand side of the last equation represents an effective average flow rate through a module, i.e. the ensemble column plus extra-column dead volume, located in the \(j\)-th section of a multicolumn chromatographic unit. Through this the effective flow rate ratio, \(\bar{m}_j\), can be defined as follows:

\[\bar{m}_j = \frac{\dot{Q}_j t^* - V\epsilon^* - V_j^D}{V(1 - \epsilon^*)} .\]  
(3.16)

As demonstrated elsewhere [20, 21], the effective flow rate ratios have to fulfill the same constraints to achieve complete separation as the flow rate ratios in the absence of extra-column dead volume, i.e. those defined in the previous section. On the other hand, the equations of the minimum switch time design are modified accordingly (note that for the sake of simplicity pressure drop in the extra-column dead column is
assumed to be negligible), thus resulting in the following relationships:

\[ t^* = \frac{\phi L^2}{\Delta P_{\text{max}}} \sum_{j=1}^{4} n_j \left[ \bar{m}_j (1 - \epsilon^*) + \epsilon^* + \frac{V_j^D}{V} \right], \tag{3.17} \]

\[ \alpha = \frac{\sum_{j=1}^{3} n_j (\bar{m}_j - \bar{m}_4) (1 - \epsilon^*)}{\sum_{j=1}^{4} n_j \left[ \bar{m}_j (1 - \epsilon^*) + \epsilon^* + \frac{V_j^D}{V} \right]} \tag{3.18} \]

The value of \( V_j^D \), i.e. the extra-column dead volume which actually has to be considered in each section for a specific experimental unit, can be determined by following the same procedure section by section as described earlier [21]. Since the I-SMB process has a unique flow rate \( Q_4 \) in step II, for all possible different column- and port-configurations mentioned in that paper, \( V_j^D \) always takes the same value in the different sections, and it consists of the sum of all the extra-column dead volumes, i.e. \( V_j^D = V_a + V_b + V_c = 0.23 \text{ mL} \) as defined in section 3.2.2.

### 3.4.3 Simulation results

In order to assess the relative performance of conventional SMB and I-SMB operation a thorough study using the equilibrium dispersive model described in section 3.3.1 has been carried out. Simulations have been carried at the operating conditions corresponding to a grid of points (at a distance of 0.04 \( m \) units) within the rectangle in the \((m_2, m_3)\) plane shown in Fig. 3.4; all simulations share the same \((m_1, m_4)\) values, whose corresponding point is also shown in Fig. 3.4. The values of the switch time \( t^* \) and of the step ratio \( \alpha \), the latter only for the I-SMB solutions, have been chosen according to the minimum switch time design without
3.4 Results

extra-column dead volume, i.e. Eqs. 3.12 and 3.13. All simulations have been carried out until attainment of cyclic steady state, when the purity of the outlet streams has been calculated according to Eq. 3.5 in order to locate the region in the \((m_2, m_3)\) plane where a certain specified purity is reached in both product streams. In this work the minimum purity has been set at 99.9\%, i.e. \(X_A, X_B \geq 0.999\). The boundary of such a region, i.e. the boundary of the real complete separation region, is shown using symbols in Fig. 3.5, where also the triangle theory boundary, i.e. the boundary of the ideal complete separation region, is plotted (solid line), i.e. the same shown in Fig. 3.4.

Four cases have been considered, namely conventional SMB and I-SMB in the six-column 1-2-2-1 and in the four-column 1-1-1-1 configurations. As readily observed in Figs. 3.5(a) and (c), when six columns are used in the case of both the conventional SMB and the I-SMB the real boundary overlaps almost entirely to the ideal boundary; this is true also very close to the tip of the triangle where performance are optimal. In the case of the four-column conventional SMB, the region where high purity can be achieved is much smaller than the complete separation region calculated through triangle theory. As expected and as shown in Fig. 3.5(b), the tip of the real triangle is much closer to the diagonal than that of the ideal triangle. Finally, Fig. 3.5(d) shows that in the case of the 1-1-1-1 I-SMB process the real boundary is very close to the ideal boundary. This proves that the four-column I-SMB process can achieve at the same operating conditions, but with two columns less, purity levels very close to those achieved by the six-column processes; alternatively it can achieve the same purity specifications with operating conditions that are only slightly different, as indicated by the difference in the position of the tip of the real triangle in Fig. 3.5(d) from those in Figs. 3.5(a) and (c). This is the key result of this analysis, and is fully in line with the
3. I-SMB chromatography: Separation of Tröger’s base enantiomers

Figure 3.5: Simulation based analysis of the purity levels achieved by the different processes depending on the position of the operating point in the \((m_2, m_3)\) plane. The lines are the boundary of the ideal triangle theory complete separation region for a total feed concentration of 1 g/L. The symbols define the boundary of the computed real complete separation region, i.e. where both product purities are above 99.9%. Simulations have been carried out in all points indicated with a (+) symbol. (a) conventional 1-2-2-1 SMB; (b) conventional 1-1-1-1 SMB; (c) 1-2-2-1 I-SMB; (d) 1-1-1-1 I-SMB.
Table 3.2: Operating conditions and separation performance of the experimental SMB and I-SMB runs; the position of the operating points in the operating parameter plane is shown in Fig. 3.6; total feed concentration is 1.0 g/L.

<table>
<thead>
<tr>
<th>Operating mode / configuration</th>
<th>Flow rate ratio</th>
<th>( m_1 )</th>
<th>( m_2 )</th>
<th>( m_3 )</th>
<th>( m_4 )</th>
<th>( t' ) (min)</th>
<th>( \alpha )</th>
<th>Flow rate (mL/min)</th>
<th>Purity (%)</th>
<th>Pr (g/Lh)</th>
<th>SC (-)</th>
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<tr>
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</tr>
<tr>
<td>I-SMB 1-1-1-1</td>
<td></td>
<td>5.92</td>
<td>1.85</td>
<td>4.74</td>
<td>1.21</td>
<td>4.25</td>
<td>0.38</td>
<td>2.32 0.31 1.74 1.10</td>
<td>93.3 99.8</td>
<td>3.21 2.74</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.94</td>
<td>1.59</td>
<td>4.40</td>
<td>1.21</td>
<td>4.12</td>
<td>0.37</td>
<td>2.51 0.20 1.69 1.11</td>
<td>100.0 94.9</td>
<td>3.23 2.77</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.94</td>
<td>1.87</td>
<td>4.37</td>
<td>1.22</td>
<td>4.18</td>
<td>0.37</td>
<td>2.43 0.34 1.62 1.11</td>
<td>100.0 99.8</td>
<td>2.95 2.90</td>
<td></td>
</tr>
</tbody>
</table>
results presented in Chapter 2 [19].

3.4.4 Experimental results

The comparative study presented above has been repeated experimentally, by carrying out 15 runs using the same processes and process configurations as above. The operating conditions, i.e. flow rate ratios, flow rates, switch time and step ratio, and the separation performance, in terms of purity, productivity and solvent consumption, of all the experimental runs are reported in Table 3.2. Each experimental run was designed according to the minimum switch time approach, while taking into account the effect of the extra-column dead volume, i.e. effective flow rate ratios are used together with Eqs. 3.17 and 3.18. Note that all flow rates and flow rate ratios reported are those measured during the experiments, also in the case where they deviated from the set points.

The position of the operating points in the \((m_2, m_3)\) and \((m_1, m_4)\) for the four different combinations of processes and unit configurations is shown in the four parts of Fig. 3.6, where also the complete separation region calculated for the bi-Langmuir isotherm at a feed concentration of 1 g/L using triangle theory is plotted. Open symbols identify runs where both product streams fulfilled the purity specification of 99.5\%, whereas filled symbols correspond to experiments where one or the other product was off-spec (see Table 3.2).

With reference to Figs. 3.6(a), (c) and (d) it can readily be observed that the six-column conventional SMB as well as both I-SMB configurations fulfill purity specifications also for operating points very close to the tip of the ideal complete separation region in the \((m_2, m_3)\) plane. As the operating point moves beyond its boundaries purity drops immediately,
3.4 Results

Figure 3.6: Operating points of the experimental runs together with the ideal triangle theory complete separation region for a total feed concentration of 1 g/L. Open symbols: operating points where purity specification are fulfilled, i.e. $X_A, X_B \geq 0.995$; filled symbols: operating points where at least one of the product stream is off-spec. (a) conventional 1-2-2-1 SMB; (b) conventional 1-1-1-1 SMB; (c) 1-2-2-1 I-SMB; (d) 1-1-1-1 I-SMB.
as expected (check Table 3.2). In contrast, the four-column conventional SMB fulfills the high purity specification only if the operating point is chosen sufficiently inside the complete separation region, as shown in Fig. 3.6(b). Comparing Fig. 3.6 and Fig. 3.5 demonstrates that the experimental performance and the simulation results are in perfect agreement.

### 3.5 Discussion and conclusions

This work demonstrates through both experiments and simulations three important features of the I-SMB technology when applied at relatively low feed concentration, i.e. under conditions where the species to be separated are subject to an adsorption isotherm exhibiting a rather mild nonlinearity.

First, the implementation of the I-SMB mode of operation on a rather standard multi column chromatographic laboratory unit is extremely simple and fully compatible with the alternate operation as conventional SMB. Moreover, the design of I-SMB separations is based on the same concepts that apply to the conventional SMB and on similarly simple criteria.

Secondly, due to its specific operation mode the I-SMB process allows for high purity separations also when implemented in a four-section 1-1-1-1 configuration, as anticipated in our earlier theoretical study [19]. This key result is further illustrated in Fig. 3.7, where the position in the \((m_2, m_3)\) plane of the experimental operating points where the four process operation and configurations considered in this study achieve the best performance, i.e. the highest productivity and the lowest solvent consumption, is shown and compared with the complete separation
3.5 Discussion and conclusions

Figure 3.7: Operating points of the best performing experimental runs for each combination of operation mode and configuration, together with the ideal triangle theory complete separation region for a total feed concentration of 1 g/L. The dotted line indicates the real boundary of the complete separation region for the 1-1-1-1 conventional SMB process (see Fig. 3.5(b)).

region calculated through triangle theory. It is rather clear that the six-column SMB process and the two configurations of the I-SMB process fulfill purity specifications at very similar operating conditions, which are quite close to the tip of the ideal complete separation region. On the contrary, the best operating point for the four-column SMB process is rather far from such conditions as discussed and clarified in Chapter 2 [19], i.e., band broadening effects on the concentration profile of each component along the columns directly lead to serious degradation of the product purity in the case of the 1-1-1-1 SMB configuration.

This observation leads to the most attractive feature of the I-SMB operation when implemented in a four-column 1-1-1-1 configuration, namely
3. I-SMB chromatography: Separation of Tröger’s base enantiomers

Figure 3.8: Separation performance in terms of productivity and solvent consumption for each combination of operation mode and configuration. Symbols are the values attained in the same best performing experimental runs shown in Fig. 3.7. Lines are the values corresponding to the operating points along the calculated boundaries of the real complete separation regions in Fig. 3.5. Note that the curves for 1-2-2-1 conventional SMB and 1-2-2-1 I-SMB overlap.

that it outperforms the six-column conventional SMB process (and the six-column I-SMB process) in terms of productivity, because the same purity levels can be attained at very similar operating conditions but with four columns instead of six. This is illustrated in Fig. 3.8, where the productivity and the solvent consumption attained in the four experimental runs considered in Fig. 3.7 are plotted together with those calculated through detailed simulations for the four process modes and configurations considered here at the operating points along the boundaries of the real complete separation regions shown in Fig. 3.5. For each configuration the calculated values define a curve consisting of two branches, converging in a tip; with reference to Figs. 3.5 and 3.7, the tip corresponds to the tip of the real complete separation region and the two branches correspond to the two parts of the boundary, i.e. the upper and the lower branch corresponding to the part of the boundary.
at roughly constant $m_3$ and $m_2$, respectively. Note that the curves for conventional SMB and I-SMB in the 1-2-2-1 configuration overlap and are indistinguishable, whereas the two branches for the conventional 1-1-1-1 SMB overlap.

The tips of the curves in Fig. 3.8 correspond to the tips of the triangles in Fig. 3.7, and to the best performance, i.e. highest productivity and lowest solvent consumption, corresponding to the assigned purity specifications. One can readily observe that at the tip of the curve corresponding to the 1-1-1-1 I-SMB the productivity is more than two times larger than at the tip of the curve corresponding to the six-column processes, whereas the solvent consumption is essentially the same. Both parameters are much better in the 1-1-1-1 I-SMB configuration than in the 1-1-1-1 SMB configuration. It is also obvious from the figure that one can indeed profit of such improved performance also in experiments, even within a study like this where no thorough tuning of the operating conditions has been carried out.

This study demonstrates that the I-SMB technology bears great promise for important applications such as the separation of enantiomers of chiral compounds, where high purity values are required and productivity is the key performance indicator, since the chromatographic media are very expensive. Further work will show that the I-SMB process indeed outperforms the conventional SMB technology also at large feed concentration where the species to be separated are clearly subject to a nonlinear adsorption isotherm [40, 41].

**Acknowledgements**

The author would like to thank Olga Kartachova for her help in some of the experiments and Dr. Christian Langel for his stimulating comments.
3. I-SMB chromatography: Separation of Tröger’s base enantiomers

Nomenclature

\( a_{i,k}, b_{i,k} \) parameters in Bi-Langmuir isotherm for component \( i \)
\( c_i \) fluid phase concentration of component \( i \)
\( c_T \) total feed concentration
\( c_{P,i} \) concentration of component \( i \) at port \( P \)
\( \bar{c}_{P,i} \) average concentration of component \( i \) at port \( P \)
\( D_i \) axial dispersion coefficient of component \( i \)
\( H_i \) Henry’s constant of component \( i \)
\( k_{s,i}a_v \) product of mass transfer coefficient and specific surface of component \( i \)
\( L \) column length
\( m_j \) flow rate ratio in section \( j \) of conventional SMB and I-SMB
\( n_i^* \) adsorbed phase concentration of component \( i \) in equilibrium with the mobile phase
\( n_j \) number of the columns in section \( j \)
\( Pr \) productivity
\( \Delta P \) pressure drop
\( Q_j \) volumetric flow rate in section \( j \)
\( \bar{Q}_j \) average volumetric flow rate in section \( j \)
\( Q_P \) volumetric flow rate at port \( P \)
\( S \) column cross-section
\( SC \) dimensionless solvent consumption
\( t \) time
\( t_0 \) hold up time
\( t^* \) switch time
\( u \) superficial velocity
\( V \) column volume
\( X_i \) product purity
3.5 Discussion and conclusions

\[ Y_i \quad \text{recovery of component } i \]
\[ z \quad \text{axial coordinate} \]

**Greek letters**

\[ \alpha \quad \text{step ratio of I-SMB} \]
\[ \epsilon^* \quad \text{overall bed void fraction} \]
\[ \epsilon_b \quad \text{inter particle void fraction} \]
\[ \phi \quad \text{pressure drop factor} \]

**Subscripts and superscripts**

\[ A \quad \text{component A} \]
\[ B \quad \text{component B} \]
\[ i \quad \text{component index} \]
\[ j \quad \text{section index} \]
3. I-SMB chromatography: Separation of Tröger’s base enantiomers
Chapter 4

I-SMB chromatography: Separation of Tröger’s base enantiomers under nonlinear conditions*

One of the modified SMB processes, the I-SMB process, has been analyzed theoretically in Chapter 2 [19] and its superior performance compared to the conventional SMB process has been demonstrated at a rather low total feed concentration through experiments and simulations in Chapter 3 [29]. This work shows that the I-SMB process outperforms the conventional SMB process also at high feed concentration.

*The content of this chapter has been submitted to the journal by Katsuo, Langel, Sandré and Mazzotti [40].
where the species are clearly subject to a nonlinear adsorption isotherm. In the case of the separation of the Tröger’s base’s enantiomers in ethanol on Chiralpak AD, the two processes operated in a six-column 1-2-2-1 configuration (one column in sections 1 and 4 and two columns in sections 2 and 3) and in a four-column 1-1-1-1 configuration (one column in each section) are compared at high feed concentration through both experiments and simulations. Even under nonlinear conditions the four column I-SMB process can successfully separate the two enantiomers achieving purity levels as high as the two six column processes and exhibiting better productivity.

4.1 Introduction

I-SMB chromatography is an extension of the conventional SMB process, which has been invented and patented by Nippon Rensui Corporation [13]. In Chapter 2 and 3 we have theoretically analyzed this process [19] and demonstrated its good performance at rather low total feed concentration when compared with that of the conventional SMB process [29].

The conventional SMB process simulates a continuous countercurrent movement of the fluid phase and of the adsorbent by periodically switching the inlet and outlet ports to a set of identical chromatographic columns in the same direction of the fluid flow; the time period between two switches is the switch time, \( t^* \). Typically a SMB unit is divided in four sections by two inlets and two outlets, in such a way that the feed and the mobile phase (desorbent) are introduced between sections 2 and 3 and between sections 4 and 1, respectively, whereas the extract (where the more retained species, labeled A in the following, is withdrawn)
is collected between sections 1 and 2 and the raffinate (containing the less retained component B) is collected between sections 3 and 4. The outlet of section 4 is recycled to section 1 in the case of the rather common closed-loop configuration, otherwise it is collected and possibly recycled off-line in the case of the open-loop configuration.

On the contrary, the I-SMB process is operated in two different modes during one switch period $t^*$, which is in fact divided into two sub-intervals. During the first step I, of duration $\alpha t^*$ ($0 < \alpha < 1$), the unit is operated as a three-section conventional SMB, where the feed and desorbent are normally introduced, the extract and the raffinate are normally collected, but there is no flow in section 4. During the second step II, the ports of the inlets and outlets are closed and the fluid is just circulated through all sections of the unit to adjust the relative position of the concentration profiles with respect to the positions of the inlet and outlet ports [19].

Its key features have been discussed in the frame of the equilibrium theory, and it has been shown that the synchronous partial feed and partial withdrawn operation of the I-SMB process makes it possible to achieve high product purity and good separation performance with four columns only [19]. The separation of the Tröger’s base’s enantiomers on Chiralpak AD stationary phases using ethanol as mobile phase has been carried out in an existing laboratory multi-column chromatography unit operated in both the I-SMB and the conventional SMB mode at rather low feed concentration where the species to be separated are subject to an adsorption isotherm exhibiting a mild nonlinearity. It has been demonstrated that indeed the four column (1-1-1-1 configuration, i.e. one column in each section) I-SMB process outperforms the conventional SMB process [29].

However, in most cases of practical interest in order to maximize pro-
ductivity one has to deal with a separation carried out under nonlinear conditions, i.e., where the species are clearly subject to a nonlinear adsorption isotherm. In this study, the potential of the I-SMB process at high feed concentration, i.e. under nonlinear conditions, will be explored through experiments as well as simulations using the same model system consisting of the Tröger’s base enantiomers on Chiralpak AD as stationary phase and in ethanol as mobile phase. The separation performance of the four-column and six-column (1-2-2-1 configuration, i.e. two columns in sections 2 and 3) I-SMB and conventional SMB processes at a total feed concentration from 5 g/L to 15 g/L will be analyzed and compared, in order to assess the potential at the I-SMB technology at high feed concentration.

4.2 Background

In this section we summarize background information from the previous chapters that are needed for the comprehension of the new material presented in this work [29].

4.2.1 Experimental setup

The laboratory multicolumn chromatography unit used in this work is a modified ÄKTA™ Explorer 100 system (GE Healthcare), where all devices, i.e. multiposition valves, pumps, and on-line detectors, are controlled by the UNICORN™ software (GE Healthcare) [21, 30]; Fig. 3.1 shows a scheme of the unit, where each section can consist of one or more (two in this case) columns. During step I of the I-SMB operating mode the raffinate valve is open so as to withdraw as raffinate product
the whole stream leaving section 3, whereas during step II the raffinate valve is closed, the two pumps at the extract and feed ports are shut off, and the desorbent pump delivers the specified flow required by the circulation of the fluid phase. In order to run the unit in the conventional SMB mode, the valve at the raffinate port is just replaced by a pump.

When designing SMB or I-SMB experiments using a small scale unit, where the volume of tubings and connections is not negligible with respect to the column volume, the effect of the extra-column dead volume has to be taken into account [20, 21, 29]. Such dead-volume consists of the parts connecting two consecutive chromatographic columns, whose volume has been determined precisely using a tracer: namely the volume from the column to the outlet manifold, \( V_b = 0.02 \text{ mL} \), that from the outlet manifold to the inlet manifold before the next column, including the check valve, \( V_c = 0.18 \text{ mL} \), and the volume from the outlet manifold to the inlet of the next column, \( V_a = 0.03 \text{ mL} \). It is worth noting that after a few experimental runs, we have inserted a small piece of tubing at the raffinate and extract ports thus changing their configuration in order to avoid possible cross contamination at outlet manifolds, which may cause the degradation of product purity. This causes an additional extra-column dead volume \( V'_b = 0.02 \text{ mL} \), which has to be considered in the four-column SMB experiments at 5 g/L feed concentration and in all experiments at 10 and 15 g/L. As long as the extra-column dead volume is properly handled, its impact on the separation performance can by and large be eliminated [21, 29].

### 4.2.2 Materials

This work studies the separation of the enantiomers of the Tröger’s base, \((\pm)-2,8\text{-dimethyl-6H,12H-5,11-methanodibenzo[b,f][1,5]}\text{diazocine}\).
Table 4.1: Chromatographic model and performance indicators [19, 29].

<table>
<thead>
<tr>
<th>Model</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromatographic model</td>
<td>( \frac{\epsilon^<em>}{\partial t} \frac{\partial c_i}{\partial t} + (1 - \epsilon^</em>) \frac{\partial n_i^<em>}{\partial t} + u \frac{\partial c_i}{\partial z} = \epsilon^</em> D_{ap,i} \frac{\partial^2 c_i}{\partial z^2} ) (i = A, B)</td>
</tr>
<tr>
<td>Bi-Langmuir isotherm</td>
<td>( n_i^* = \frac{a_{i,1} c_i}{1 + \sum_j b_{j,1} c_j} + \frac{a_{i,2} c_i}{1 + \sum_j b_{j,2} c_j} ) (i = A, B)</td>
</tr>
<tr>
<td></td>
<td>( H_A = a_{A,1} + a_{A,2} &gt; a_{B,1} + a_{B,2} = H_B )</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average concentration (^{a,b})</td>
<td>( \bar{c}<em>{P,j} = \frac{1}{\alpha t^*} \int</em>{N_p}^{\alpha(N+a)t^*} c_{P,j} dt )</td>
</tr>
<tr>
<td>Product purity</td>
<td>( X_A = \frac{\bar{c}<em>{E,A}}{\bar{c}</em>{E,A} + \bar{c}<em>{E,B}} \quad X_B = \frac{\bar{c}</em>{R,B}}{\bar{c}<em>{R,A} + \bar{c}</em>{R,B}} )</td>
</tr>
<tr>
<td>Recovery</td>
<td>( Y_A = \frac{Q_E \bar{c}<em>{E,A}}{Q_F c</em>{F,A}} \quad Y_B = \frac{Q_R \bar{c}<em>{R,B}}{Q_F c</em>{F,B}} )</td>
</tr>
<tr>
<td>Productivity (^b)</td>
<td>( Pr = \frac{\alpha(Q_E \bar{c}<em>{E,A} + Q_R \bar{c}</em>{R,B})}{\sum n_j V} )</td>
</tr>
<tr>
<td>Solvent consumption</td>
<td>( SC = \frac{(Q_D + Q_F)}{Q_F(Y_A c_{F,A} + Y_B c_{F,B})} )</td>
</tr>
</tbody>
</table>

\(^a\) The index P identifies the products stream.
\(^b\) \( \alpha \) must be taken as 1 in conventional SMB.
This compound has often been used in chiral chromatography studies [31–36]. According to the characterization of the phase behavior and of the solid-liquid equilibrium of the Tröger’s base enantiomers in ethanol, the solubility of the racemate at room temperature is about 18 g/L [37].

The racemic mixture of Tröger’s base was purchased from Sigma Aldrich; Chiralpak AD (Chiral Technologies Europe) was used as chiral stationary phase and ethanol (Merck, Scharlau) as mobile phase. The competitive adsorption behavior of the system was investigated by applying the inverse method as reported in Chapter 3 [29]; it can be described accurately enough by the bi-Langmuir adsorption isotherm given in Table 4.1. The method used for the isotherm parameters determination allows at the same time to estimate the dispersion coefficient as well; such model parameters are reported in Table 3.1.

### 4.2.3 Mathematical model

Both the conventional SMB and the I-SMB processes can be described by coupling single chromatographic column models (one for each column in the unit) with proper material balances at the nodes between the columns according to the specific operating mode and port switching mechanism. The classical equilibrium dispersive model is used for each chromatographic column in this work [22–24]. The details about the model have been discussed in Chapter 2 and are summarized in Table 4.1; all parameters used in the model and the column characteristics are given in Table 3.1 [19, 29].
4.2.4 Separation performance indicators

For the assessment of the separation performance a number of indicators has been introduced, as summarized in Table 4.1 [29]. Based on the average concentration of component \( i \) (\( i = A,B \)) at each product stream, \( \bar{c}_{P,i} \) (the index \( P \) identifies the product stream), over the product recovery time in one switch period, i.e. \( t^* \) in the case of the conventional SMB process, and \( \alpha t^* \) in the case of the I-SMB process, the product purities \( X_i \) are defined. The productivity, \( Pr \), which may be the most important indicator from an economical point of view, is defined as the total amount of recovered products per unit volume of the stationary phase per unit time. Another important performance indicator is the solvent consumption per unit amount of recovered products, \( SC \), which is not in dimensionless form due to the presence of the feed concentration in the denominator, in order to compare the performance of separations operated at different feed concentrations.

4.2.5 Design of the operating conditions

Under linear chromatographic conditions, i.e. low or very low feed concentration, the well known design criteria of the conventional SMB process, the so-called triangle theory, have been extended to the I-SMB process, as presented and discussed in detail in Chapter 2 and 3 [19, 29]. Although the adsorption isotherm considered here exhibits clear nonlinear behavior, such design concept based on the flow rate ratios is considered to be still useful and applicable. As shown in Table 4.2, the flow rate ratio in section \( j \), \( m_j \), is defined based on the average flow rate in section \( j \), \( \hat{Q}_j \), which coincides with the flow rate in section \( j \) in the case of the conventional SMB unit, but has to be calculated accounting
4.2 Background

Table 4.2: Minimum switch time design concepts [19, 29].

| Average flow rate (I-SMB) | \( \hat{Q}_j = \alpha Q_j + (1 - \alpha)Q_4 \quad (j = 1, 2, 3), \)
| | \( \hat{Q}_4 = (1 - \alpha)Q_4 \)
| (Conventional SMB) | \( \hat{Q}_j = Q_j \quad (j = 1, ..., 4) \)

For a unit without extra-column dead volume

Flow rate ratio

\[ m_j = \frac{\hat{Q}_j t^* - Ve^*}{V(1 - e^*)} \quad (j = 1, ..., 4) \]

Minimum switch time

\[ t^* = \frac{\phi L^2}{\Delta P_{\text{max}}} \sum_{j=1}^{4} n_j \left( m_j (1 - e^*) + e^* \right) - \sum_{j=1}^{3} n_j \left( m_j - m_4 \right) (1 - e^*) \]

Step ratio (I-SMB only)

\[ \alpha = \frac{\sum_{j=1}^{4} n_j \left( m_j (1 - e^*) + e^* \right)}{\sum_{j=1}^{4} n_j \left( m_j (1 - e^*) + e^* \right) + V_j V_4} \]

For a unit with extra-column dead volume \(^a\)

Effective flow rate ratio

\[ m_j = \frac{\hat{Q}_j t^* - Ve^* - V_j^D}{V(1 - e^*)} \quad (j = 1, ..., 4) \]

Minimum switch time

\[ t^* = \frac{\phi L^2}{\Delta P_{\text{max}}} \sum_{j=1}^{4} n_j \left[ \bar{m}_j (1 - e^*) + e^* + \frac{V_j^D}{V} \right] - \sum_{j=1}^{3} n_j \left( \bar{m}_j - \bar{m}_4 \right) (1 - e^*) \]

Step ratio (I-SMB only)

\[ \alpha = \frac{\sum_{j=1}^{4} n_j \left[ \bar{m}_j (1 - e^*) + e^* + \frac{V_j^D}{V} \right]}{\sum_{j=1}^{4} n_j \left[ \bar{m}_j (1 - e^*) + e^* + \frac{V_j^D}{V} \right]} \]

\(^a\) The value of \( V_j^D \), which has to be considered in each section of a specific experimental unit, should be properly handled following the instructions discussed in the earlier works [21, 29].
for the two sub-intervals of the switch period in the I-SMB case. As demonstrated in the next section through comprehensive simulations, it is possible to choose the values of the flow rate ratios that allow to achieve complete separation for both SMB and I-SMB separations also in the case of nonlinear chromatographic conditions. The additional parameters needed to define the operating conditions in the unit, namely the switch time $t^*$ and the parameter $\alpha$, the latter only in the I-SMB case, can be determined by enforcing the pressure drop constraint to the system, i.e. by applying the so-called minimum switch time design [19].

In the case of experiments using a small scale unit where the volume of tubings and connections is not negligible compared to the column volume, the operating conditions are determined in terms of the effective flow rate ratios $\bar{m}_j$ taking into account the effect of the extra-column dead volume $V_j^D$ (see the corresponding definitions in Table 4.2). Accordingly the minimum switch time design is modified. The value of $V_j^D$, which has to be considered in each section of a specific experimental unit, should be properly determined following the instructions discussed in detail in earlier works [21, 29]. The actual volume of each tubing parts of the unit used in this work has already reported in the previous section.

### 4.3 Choice of the operating conditions for nonlinear I-SMB processes

For both the conventional SMB and the I-SMB process under linear chromatographic conditions, the choice of the flow rate ratios to achieve the complete separation of the two species to be separated is based on the same explicit criteria, i.e. those given by triangle theory, namely $m_1 \geq H_A \geq m_3 \geq m_2 \geq H_B \geq m_4 \geq -\epsilon^*/(1 - \epsilon^*)$, where $H_A$ and $H_B$ are
4.3 Choice of the operating conditions for nonlinear I-SMB processes

the Henry’s constants of the two species in the feed mixture. This is based on a rigorous demonstration that is indeed possible in the linear case [19].

For the conventional SMB separation of binary mixtures subject to a nonlinear adsorption isotherm, the design criteria for the choice of the flow rate ratios have been developed for the generalized Langmuir isotherm [15, 42, 43], and for more general cases including the bi-Langmuir isotherm [39]. Such equilibrium theory based analysis yields criteria on the flow rate ratios, which are not so simple as in the linear case, but still lead to explicit (in the case of the generalized Langmuir isotherm) or rather simple (in the case of the bi-Langmuir isotherm) equations for the boundaries of the complete separation region in the operating parameter space, in terms of the feed composition and of the adsorption isotherm parameters. Particularly simple and useful is the graphical representation of the complete separation region in the \((m_2, m_3)\) plane, which is no longer the right triangle of the linear case but gets more and more distorted as the feed concentration increases. This is shown in Fig. 4.1 for the specific bi-Langmuir adsorption isotherm used in this work to describe the Tröger’s base’s enantiomers, in the most obvious case of a racemic feed mixture. As expected the complete separation region in the \((m_2, m_3)\) plane shrinks and the theoretical optimal operating point, i.e. the tip of the region, moves downwards and to the left. In the same figure the corresponding complete separation region in the \((m_1, m_4)\) plane is also shown (rectangle in the lower right corner). Note that while the lower bound on \(m_1\) is defined explicitly, the actual upper bound on \(m_4\) depends on the values of \(m_2\) and \(m_3\) chosen for the specific operation; for the sake of simplicity the boundary shown in the figure is calculated for the \(m_2\) and \(m_3\) values of the vertex of the corresponding complete separation region in the \((m_2, m_3)\) plane.
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Figure 4.1: Triangle theory complete separation region for the separation of the Tröger’s base enantiomers. Linear triangle and regions calculated for the bi-Langmuir isotherm at different total feed concentrations, i.e. 1, 5, 10 and 15 g/L. The upper bound for $m_4$ is calculated for the $m_2$ and $m_3$ values corresponding to the tip of the complete separation region. The symbol (○) identify $m_1$ and $m_4$ values where simulations have been carried out.
4.3 Choice of the operating conditions for nonlinear I-SMB processes

4.3.1 Complete separation region for nonlinear I-SMB processes

On the other hand, for the nonlinear I-SMB separation no criteria for the choice of the flow rate ratios to achieve complete separation have been derived yet. Based on intuition and physical similarity, we have conjectured that the same situation as in the linear case occurs, i.e. that also under nonlinear chromatographic conditions it is possible to apply the same criteria used for the conventional SMB also to the I-SMB. However, since there is no theoretical demonstration, only a comprehensive simulation study can provide confidence that such extension of the triangle theory makes sense and is accurate.

Fig. 4.2 illustrates the results of such study, where simulations for the six column 1-2-2-1 I-SMB process at four different total feed concentrations, i.e. 1, 5, 10 and 15 g/L, have been carried out at the operating conditions corresponding to a grid of points (indicated by the + symbols in the figure) within the rectangle in the \((m_2, m_3)\) plane around the tip of the corresponding complete separation regions calculated according to triangle theory (see Fig. 4.1) and for constant values of the other two flow rate ratios, namely \(m_1 = 6\) and \(m_4 = 1.2\) (see the open circle in the lower right corner of Fig. 4.1). The values of the switch time \(t^*\) and of the step ratio \(\alpha\) have been chosen according to the minimum switch time design without extra-column dead volume. Under the cyclic steady state of each simulation run the purity of the two product streams is calculated according to the equation in Table 4.1, hence to each point in the grid of operating points a pair of purity values is associated. Based on this purity landscape, it is possible to identify the region where the I-SMB process delivers products fulfilling a certain purity specification, which has been chosen to be 99.9% purity in this case, i.e. \(X_A, X_B \geq 0.999\). In
4. I-SMB chromatography: Separation of Tröger’s base enantiomers under nonlinear conditions

Figure 4.2: Simulation based analysis of the purity levels achieved by the 1-2-2-1 I-SMB depending on the position of the operating point in the \((m_2, m_3)\) plane. The lines are the boundary of the ideal triangle theory complete separation region. The symbols define the boundary of the computed real complete separation region, i.e. where both product purities are above 99.9%. Simulations have been carried out in all points indicated with a (+) symbol. (a) \(c_F^T = 1.0\) g/L; (b) \(c_F^T = 5.0\) g/L; (c) \(c_F^T = 10.0\) g/L; (d) \(c_F^T = 15.0\) g/L.
Fig. 4.2 the boundary of such region, i.e. the boundary of the *real* complete separation region of the I-SMB process, is shown using symbols together with the constraints derived by triangle theory, i.e. the *ideal* complete separation boundary, plotted as a solid line. As observed in all four subfigures of Fig. 4.2, the *real* complete separation boundary of the 1-2-2-1 I-SMB process and the *ideal* boundary are identical within the precision offered by the fineness of the chosen grid of operating points. A similar result, which is not shown here for the sake of brevity, has been obtained for feed concentrations up to 18 g/L, i.e. the solubility limit of the racemic mixture.

These results demonstrate that the same criteria derived from the nonlinear triangle theory for conventional SMB separations can be applied also to I-SMB processes operated under nonlinear chromatographic conditions, at least in the case of a six-column I-SMB unit in the 1-2-2-1 configuration.

### 4.3.2 Comparison of conventional SMB and I-SMB processes

A similar simulation study has been carried out for different column configurations (six-column 1-2-2-1 and four-column 1-1-1-1) of the conventional SMB process and of the I-SMB process, all operated at 5 g/L of overall feed concentration, i.e. under nonlinear chromatographic conditions. Fig. 4.3 illustrates the results of the four resulting cases, using the same graphical conventions utilized for Fig. 4.2; note that Fig. 4.3(c) is the same as Fig. 4.2(b), and it is shown again here for comparison. As seen in Figs. 4.3(a) and (c), when six columns are used, the *real* boundary of the complete separation region for both conventional SMB and I-SMB practically overlaps the *ideal* boundary. On the contrary, in the case of
4. I-SMB chromatography: Separation of Tröger’s base enantiomers under nonlinear conditions

Figure 4.3: Simulation based analysis of the purity levels achieved by the different processes depending on the position of the operating point in the \((m_2, m_3)\) plane. The lines are the boundary of the ideal triangle theory complete separation region for a total feed concentration of 5 g/L. The symbols define the boundary of the computed real complete separation region, i.e. where both product purities are above 99.9%. Simulations have been carried out in all points indicated with a (+) symbol. (a) conventional 1-2-2-1 SMB; (b) conventional 1-1-1-1 SMB; (c) 1-2-2-1 I-SMB; (d) 1-1-1-1 I-SMB.
the four-column conventional SMB process the real complete separation region is much smaller than the ideal one, as shown in Fig. 4.3(b). This is a well known effect of the fact that with only four columns the conventional SMB process simulates the countercurrent movement of the fluid and the solid in an unsatisfactory manner, and therefore the real separation performance is significantly worse than what predicted by the triangle theory, which is based on assuming that such countercurrent contact is perfectly reproduced. On the contrary, the real boundary of the four column I-SMB process is very close to the ideal boundary, as shown in Fig. 4.3(d). This is exactly what was already observed in Chapter 3, in the case of separations at rather low feed concentration where the isotherm is linear or exhibits mild nonlinearity [29]. Note that the same qualitative conclusions are reached when repeating the same simulations for an overall feed concentration up to 18 g/L.

These results demonstrate that the same criteria derived from the nonlinear triangle theory for conventional SMB separations can be applied also to four-column I-SMB processes operated under nonlinear chromatographic conditions, but not to four-column conventional SMB processes. This is a very important result, because it shows that the same purity performance can be achieved in a four-column I-SMB unit as in a six-column SMB or I-SMB unit, thus leading to higher productivity.

4.4 Experimental results and discussion

In order to confirm the conclusions of the simulation study, about 20 experiments have been carried out. All four operating modes considered so far, i.e. six-column and four-column SMB and I-SMB processes, have been tested with a feed mixture of 5 g/L total concentration, whereas at
Table 4.3: Operating conditions and separation performance of the experimental SMB and I-SMB runs; the position of the operating points in the operating parameter plane is shown in Figs. 4.4, 4.5, and 4.6.

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<th>Flow rate (mL/min)</th>
<th>Purity (%)</th>
<th>Raffinate</th>
<th>Extract</th>
<th>Pr (g/Lh)</th>
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the higher feed concentrations of 10 and 15 g/L only the four-column processes have been studied. The operating conditions and the separation performance in terms of purity, productivity and solvent consumption, of all the experimental runs are reported in Table 4.3. Each experimental run was designed according to the minimum switch time approach, while taking into account the effect of the extra-column dead volume. Note that all flow rates and flow rate ratios reported in the table are those measured during the experiments, also in the case where they deviated from the set points.

4.4.1 Product purity

In Fig. 4.4 the operating points on the \((m_2, m_3)\) and \((m_1, m_4)\) planes of the experiments at 5 g/L feed concentration in different process configurations are shown together with the ideal complete separation boundaries calculated according to the triangle theory. Similarly, the operating points of the experiments using only four columns at the higher feed concentrations of 10 and 15 g/L are plotted in Figs. 4.5 and 4.6, respectively, together with the corresponding ideal complete separation regions. Open symbols represent operating points of the experiments, where both extracts and raffinate have been obtained at a purity above the specification, i.e. 99.5%, which is a very high purity for this type of separations. Filled symbols refer to experimental runs where one product stream, or the other, or both was out of specs.

The key conclusion is that the experimental results are fully consistent with the outcome of the simulation studies presented above. Figs. 4.4(a) to (d) for experiments at 5 g/L feed concentration show clearly that high purity separation can be achieved at operating points very close to the tip of the ideal complete separation region in the case of all processes, but
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Figure 4.4: Operating points of the experimental runs together with the ideal triangle theory complete separation region for a total feed concentration of 5 g/L. Open symbols: operating points where purity specification are fulfilled, i.e. $X_A, X_B \geq 0.995$; filled symbols: operating points where at least one of the product streams is off-spec. (a) conventional 1-2-2-1 SMB; (b) conventional 1-1-1-1 SMB; (c) 1-2-2-1 I-SMB; (d) 1-1-1-1 I-SMB.
4.4 Experimental results and discussion

Figure 4.5: Operating points of the experimental runs together with the ideal triangle theory complete separation region for a total feed concentration of 10 g/L. Open symbols: operating points where purity specification are fulfilled, i.e. $X_A, X_B \geq 0.995$; filled symbols: operating points where at least one of the product streams is off-spec. (a) conventional 1-1-1-1 SMB; (b) 1-1-1-1 I-SMB.

The 1-1-1-1 SMB process, which has to be operated far from the tip, i.e. well inside the complete separation region calculated through triangle theory, in order to fulfill the purity specifications. The comparison of the purity results obtained at 10 and 15 g/L feed concentration using the four-column SMB and I-SMB processes and shown in Figs. 4.5 and 4.6 confirm these conclusions and allow to extrapolate them to any feed concentration and degree of nonlinearity of the adsorption isotherms.

Let us consider more in detail the 1-1-1-1 I-SMB process, since this is the most promising in terms of purity and productivity. In particular, let us consider the effect of the position of the operating point in the $(m_2, m_3)$ plane relative to the real complete separation region on the purity of the two product streams. This is illustrated for different levels
4. I-SMB chromatography: Separation of Tröger’s base enantiomers under nonlinear conditions

Figure 4.6: Operating points of the experimental runs together with the ideal triangle theory complete separation region for a total feed concentration of 15 g/L. Open symbols: operating points where purity specification are fulfilled, i.e. $X_A, X_B \geq 0.995$; filled symbols: operating points where at least one of the product streams is off-spec. (a) conventional 1-1-1-1 SMB; (b) 1-1-1-1 I-SMB.

of the feed concentration in Figs. 4.7 (a), (b) and (c), where the symbols indicate the experimentally obtained purities. On the left (right) hand side the raffinate purity is plotted as a function of $m_3$ ($m_2$) at constant value of $m_2$ ($m_3$); these conditions correspond to operating points along the thin vertical (horizontal) solid lines in Figs. 4.4(d), 4.5(b) and 4.6(b). These figures show that the experimental purities are consistent with the simulation results and with the triangle theory not only when complete separation is achieved (open symbols in Fig. 4.7), but also when one or the other product stream is polluted with the undesired enantiomer.

These results provide the experimental confirmation that the triangle theory developed for conventional SMB processes can be applied to the design of nonlinear I-SMB separations also in cases, such as the
4.4 Experimental results and discussion

Figure 4.7: Raffinate and extract purity cuts along fixed \( m_2 \) and \( m_3 \) lines of the 4 column I-SMB separation at different feed concentration. (a) \( c_F^T = 5 \) g/L, (b) \( c_F^T = 10 \) g/L, (c) \( c_F^T = 15 \) g/L. Solid lines: simulation results along fixed \( m_2 \) (Raffinate) and \( m_3 \) (Extract) lines which locations are indicated in Fig. 4.4(d), 4.5(b) and 4.6(b); Open symbols: experimental results where purity specification are fulfilled; filled symbols: experimental results where at least one of the product streams is off-spec.
4.4.2 Separation performance

In Figs. 4.8 (a) and (b) the separation performance of the four different processes, i.e. the productivity and the solvent consumption of the four and six column conventional SMB and I-SMB processes, are plotted as functions of the total feed concentration. Symbols represent the best separation performance achieved experimentally while fulfilling the product specifications. For all unit configurations data are available.
4.4 Experimental results and discussion

at feed concentrations of 1 g/L (from Chapter 3 [29]) and at 5 g/L (from Table 4.3); at 10 and 15 g/L feed concentration experimental data are available only for the four-column I-SMB process. The 1-1-1-1 conventional SMB experiments at high feed concentration have been carried at operating points very close to those of the 1-1-1-1 I-SMB to show that these do not achieve purity specs under those conditions. As a consequence for the four-column conventional SMB process at 10 and 15 g/L feed concentration we cannot show performance values to be plotted in Fig. 4.8.

The lines represent the performance calculated by running simulations at different feed concentrations for operating conditions at the tip of the real complete separation regions calculated as illustrated in Figs. 4.2 and 4.3; note that the lines for the six column conventional SMB and I-SMB processes overlap. As well known, the higher the feed concentration, the higher the productivity and the lower the solvent consumption. As expected, in the whole feed concentration range, the four column 1-1-1-1 I-SMB process exhibits the best performance of all, by doubling the productivity of the six column 1-2-2-1 conventional SMB and I-SMB processes and achieving the same solvent consumption. Note that these simulation results correspond to the optimal performance of the four processes considered.

On the other hand, the experimental data are not the result of a detailed optimization, because of the rather small number of experiments for each process configuration at each feed concentration level explored. Nevertheless, the experimental data and the simulation results in Fig. 4.8 are remarkably consistent, particularly in terms of the trends exhibited. The difference in productivity and solvent consumption values between experiments and simulations stems from the fact that the operating conditions are not the same. If the simulations were repeated at exactly
Figure 4.9: Productivity cuts along fixed $m_2$ and $m_3$ lines of the 4 column I-SMB separation at different feed concentrations. (a) $c_F^T = 5$ g/L, (b) $c_F^T = 10$ g/L, (c) $c_F^T = 15$ g/L. Solid lines: simulation results along fixed $m_2$ and $m_3$ lines which locations are indicated in Figs. 4.4(d), 4.5(b) and 4.6(b); Open symbols: experimental results where purity specification are fulfilled; filled symbols: experimental results where at least one of the product streams is off-spec.
the same operating conditions of the experiments the results would be much closer, namely similar to what shown in Fig. 4.7 with reference to purity; we have verified this, and the results are shown in Fig. 4.9.

The combination of simulation and experimental results presented for the first time in this work demonstrates the high potential of the I-SMB technology, particularly of the 1-1-1-1 I-SMB process, for nonlinear continuous chromatographic separations. An example of such a separation for a pharmaceutically relevant compound has been recently reported [41]. Although the I-SMB process has so far been applied to separations in the sugar industry only, where adsorption isotherms are rather linear, we believe that the application of the I-SMB technology should be extended to nonlinear continuous chromatographic separations where the systems of interest are subjected to nonlinear adsorption isotherms, as it is the case in chiral separations [5].

Nomenclature

\(a_{i,k}, b_{i,k}\) parameters in bi-Langmuir isotherm for component \(i\)

\(c_i\) fluid phase concentration of component \(i\)

\(c_T^T\) total feed concentration

\(c_{P,i}\) concentration of component \(i\) at port \(P\)

\(\bar{c}_{P,i}\) average concentration of of component \(i\) at port \(P\)

\(D_i\) axial dispersion coefficient of component \(i\)

\(H_i\) Henry’s constant of component \(i\)

\(k_{s,i}a_v\) product of mass transfer coefficient and specific surface of component \(i\)

\(L\) column length

\(m_j\) flow rate ratio in section \(j\) of conventional SMB and I-SMB
4. I-SMB chromatography: Separation of Tröger’s base enantiomers under nonlinear conditions

\( n_i^* \) adsorbed phase concentration of component \( i \) in equilibrium with the mobile phase

\( n_j \) number of the columns in section \( j \)

\( Pr \) productivity

\( \Delta P \) pressure drop

\( Q_j \) volumetric flow rate in section \( j \)

\( \hat{Q}_j \) average volumetric flow rate in section \( j \)

\( Q_P \) volumetric flow rate at port \( P \)

\( S \) column cross-section

\( SC \) dimensionless solvent consumption

\( t \) time

\( t^* \) switch time

\( u \) superficial velocity

\( V \) column volume

\( X_i \) product purity

\( Y_i \) recovery of component \( i \)

**Greek letters**

\( \alpha \) step ratio of I-SMB

\( \epsilon^* \) overall bed void fraction

\( \epsilon_b \) inter particle void fraction

\( \phi \) pressure drop factor

**Subscripts and superscripts**

\( A \) component A

\( B \) component B

\( i \) component index
4.4 Experimental results and discussion

\[ j \quad \text{section index} \]
4. I-SMB chromatography: Separation of Tröger’s base enantiomers under nonlinear conditions
Chapter 5

I-SMB chromatography: On-line optimizing control

I-SMB process is one of the standard SMB modifications being widely applied in the sugar industries. In Chapter 3 and 4 the I-SMB performance was demonstrated experimentally as well as through simulations and it is shown that the four-column I-SMB outperforms the conventional SMB process.

Although, it is still common practice to run this type of multi-column continuous process sub-optimally since close to optimal conditions the operation is less robust, and there has been a lot of effort to develop a proper control scheme that exploits full economic potential of the process [5]. In this chapter, the possibility of an on-line optimizing control of the I-SMB process is studied. Taking advantage of the existing standard SMB controller [16, 17, 44, 45], on-line optimizing control of the I-SMB process is demonstrated through simulations using a virtual
5.1 Introduction

SMB chromatography is recognized as a favorable option for the separation of enantiomers, bio-related products and so on, because of its high productivity compared to the single column chromatography. However, a number of reasons cause less robust operation of the SMB separation under the optimal conditions where the best performance of the unit is expected, e.g., uncertainty on the information of the system characteristics such as adsorption isotherms which is normally determined through experiments, variation of the physical parameters among the columns, change of the environmental conditions during the operation, aging of the system and so on. Recently, to overcome the difficulties and exploit full economic potential of the SMB process, several on-line controlling techniques have been proposed [5].

On the other hand, there has been a continuous effort to develop modified SMB schemes that allow higher productivity [5, 9–12, 19]. These modified schemes still have the difficulties mentioned above, and there seems to be no simple way to apply the existing SMB controller because many of the controllers require rather precise process information. The modified schemes are totally different from the original one however they are derivatives from the conventional SMB process.

I-SMB process, one of such modified SMB schemes, has been analyzed and demonstrated experimentally as well as through simulations to show its excellent performance [19, 29, 40]. One of the benefits of this process is that the well-established design criteria for the standard SMB,
5.2 Cycle to cycle control of the I-SMB process

Figure 5.1: Scheme of SMB ‘cycle to cycle’ control concept.

namely Triangle Theory, is applicable both in case of linear and non-linear separations, and moreover there exists the equivalent operating conditions between the I-SMB and the standard SMB process.

This study seeks the possibility of on-line optimizing control of the I-SMB process by applying the existing standard SMB controller developed in the research group at ETH Zurich [16, 17, 44, 45], focusing on the feature of the process mentioned above.

5.2 Cycle to cycle control of the I-SMB process

5.2.1 Control concept

Contrary to many other control approaches, the controller developed at ETH Zurich is based on very limited information about the system under consideration, only Henry’s constants of the two species to be separated
and an average value of the column void fractions, and requires minimal tuning [16, 17, 44, 45]. During the last decade the optimizing SMB controller has been demonstrated through simulations using a virtual SMB unit for systems subject to linear and nonlinear isotherms [17, 45, 46]. And from the experimental point of view, the controller has been successfully applied to the chiral separations [18, 47].

Fig. 5.1 represents the scheme of the optimizing SMB control on a cycle-to-cycle basis. Control variables are the flow rates of section $Q_{SMB}^j$ ($j = 1, ..., 4$), and updated only once every SMB cycle based on the information of the average outlet compositions over one entire cycle [16]. The controller guides the process as it provides higher productivity and lower solvent consumption maintaining the required product specifications, i.e. the product purities, and satisfying the certain process constraints such as total pressure drop of the unit by dynamically solving the optimization problem applying Repetitive Model Predictive Control (RMPC), detail of which is given in elsewhere [17, 44]. Note again that the SMB process model used in RMPC is a very simple locally linearized one, which requires only Henry’s constants of the species to be separated and the averaged value of the column void fraction. Even in case of nonlinear separation the controller can successfully find the optimal operating conditions without any knowledge of the system nonlinearity [18].
5.2 Cycle to cycle control of the I-SMB process

5.2.2 Equivalence between I-SMB and conventional SMB

For the sake of simplicity, let us consider two components A and B subject to a linear adsorption isotherm:

\[ n^*_i = H_i c_i \quad (i = A, B), \]
\[ H_A > H_B, \]  

where for each component \( i \) \( H_i \) is its Henry’s constant, whereas \( c_i \) is its concentration in the fluid phase and \( n^*_i \) is its adsorbed phase concentration in equilibrium with the fluid phase.

For the conventional SMB process, operating conditions can be sorted in terms of the flow rate ratio of each SMB section:

\[ m^\text{SMB}_j = \frac{Q^\text{SMB}_j t^* - V_\epsilon^*}{V(1 - \epsilon^*)} \quad (j = 1, ..., 4). \]

And it is well known that the complete separation constraints are given by the following inequalities, namely Triangle Theory \([15, 48]\):

\[ H_A \leq m_1, \]
\[ H_B \leq m_2 \leq H_A, \]
\[ H_B \leq m_3 \leq H_A, \]
\[ m_4 \leq H_B, \]

where \( V \) is the column volume and \( \epsilon^* \) is the column overall void fraction.
Also for the I-SMB, based on the average flow rate ratios

\[ m_j^{I-SMB} \equiv \frac{\hat{Q}_j^{I-SMB} t^* - V \epsilon^*}{V(1 - \epsilon^*)} , \]  

(5.4)

defined by the average flow rate of each I-SMB section, \( \hat{Q}_j^{I-SMB} \equiv \alpha Q_j^{I-SMB} + \beta Q_4^{I-SMB} \) \((j = 1, 2, 3)\), \( \hat{Q}_4^{I-SMB} \equiv \beta Q_4^{I-SMB} \), its complete separation constraints are given in the same form (Eq. 5.3) as discussed in Chapter 2 [19].

According to the minimum switch time design mentioned in Chapter 2 [19], when applying the same flow rate ratio values and pressure drop constraint \( P_{total} \) for both an I-SMB and a conventional SMB unit which have the same column configuration, i.e. \( m_j^{SMB} = m_j^{I-SMB} \) and \( P_j^{SMB} = P_j^{I-SMB} \), the switch time of both processes is given as follows and the same throughput can be expected [19, 29, 40]:

\[ t^*_{total} = t^*_{I-SMB} = \frac{\phi L^2}{P_{total}} \sum_{j=1}^{4} n_j (m_j(1 - \epsilon^*) + \epsilon^*) , \]  

(5.5)

where \( L \) is the column length, and \( \phi \) is the pressure drop factor in Darcy’s law, i.e. \( \Delta P/L = \phi u \). This means that for conventional SMB process operated under the certain conditions one unique equivalent I-SMB process can be designed, and its operating conditions can be calculated as follows:

- **Given SMB operating conditions**

\[ t^*_{SMB}, \ m_j^{SMB} \ \text{(j = 1, ..., 4)}. \]  

(5.6)
5.2 Cycle to cycle control of the I-SMB process

![Diagram of control scheme]

Figure 5.2: 'Cycle to cycle' control scheme modified for the I-SMB process.

- Equivalence between I-SMB and conventional SMB

\[ t^* = t^*_{I-SMB} = t^*_{SMB}, \]
\[ m_j = m^I_{I-SMB} = m^I_{SMB} \quad (j = 1, ..., 4). \]  

(5.7)

- Equivalent I-SMB operating conditions

\[
\begin{cases}
\alpha = \frac{\sum_{j=1}^3 n_j (m_j - m_4)(1 - \epsilon^*)}{\sum_{j=1}^4 n_j (m_j(1 - \epsilon^*) + \epsilon^*)}, & \beta = 1 - \alpha, \\
Q^I_j = \frac{(m_j - m_4) V(1 - \epsilon^*)}{\alpha t^*} & (j = 1, 2, 3), \\
Q^I_4 = \frac{m_4 V(1 - \epsilon^*) + V\epsilon^*}{\beta t^*}.
\end{cases}
\]  

(5.8)

This relationship Eqs. 5.6, 5.7 and 5.8 makes it possible to apply the existing standard SMB controller to the I-SMB unit.
In Fig. 5.2, the possible scheme of the I-SMB optimizing control using the existing standard SMB controller is shown. The switch time $t^*$ is fixed. In the I-SMB unit every cycle the product purities are determined by certain methods [18, 47], and based on the information the SMB controller calculates the operating conditions of the next cycle, i.e. the four flow rates of the conventional SMB which is modeled in the controller. Then according to Eq. 5.8 the parameters are converted to the equivalent I-SMB operating conditions, i.e. four flow rates $Q_{I-SMB}^j$ and the duration of step I $\alpha t^*$, which should be sent to the controlled I-SMB plant.

In a precise sense I-SMB and conventional SMB are totally different processes and their dynamic behaviors are also different [19]. Although, the existing optimizing controller for conventional SMB is supposed to work with I-SMB separation, because of the fact that both processes can be treated equally on the same flow rate ratio plane, and because of the flexibility of the SMB controller which can successfully control the variety of the nonlinear separations only with the locally linearized model and the minimum information of the system.

5.2.3 Optimization problem formulation

Throughout the operation the controller tries to seek the operating conditions which provide the products fulfilling the specification and maximize the performance of the unit in terms of a predefined objective function while satisfying all required process constrains. The constraints and the objective function are formulated as a Linear Programming (LP) problem described briefly as follows. Detail of the formulation can be found in the literature [17].
Constraints

The purity of each product stream, which is the quantity of interest in most cases, is defined as:

\[
X_A = \frac{\bar{c}_{E,A}}{\bar{c}_{E,A} + \bar{c}_{E,B}}, \quad X_B = \frac{\bar{c}_{R,B}}{\bar{c}_{R,A} + \bar{c}_{R,B}},
\]

(5.9)

where \(\bar{c}_{E,i}\) and \(\bar{c}_{R,i}\) are the average concentration of each component in the extract and the raffinate stream, respectively. In the LP problem to be solved, the purity requirements are formulated introducing small slack variables \(s_k\):

\[
X_A \geq X_{A,\text{min}} - s_1, \quad s_1 \geq 0,
\]

(5.10)

\[
X_B \geq X_{B,\text{min}} - s_2, \quad s_2 \geq 0.
\]

From the practical aspects, process constraints such as allowable maximum pressure drop to avoid the deterioration of the packing, and prevention of the disturbance in the system induced by the radical change of the operating conditions, can be implemented as follows:

\[
P_{\text{total}} \leq P_{\text{max}},
\]

(5.11)

\[
|\Delta Q| \leq s_3.
\]

(5.12)

In the equations \(\Delta Q = [\Delta Q_1, \Delta Q_2, \Delta Q_3, \Delta Q_4]^T\) is the change of the flow rate in each SMB section over the port switch, and \(s_3\) is a set of corresponding slack variables.

In case of I-SMB separation an additional constraint in terms of the average flow rate ratios exists:

\[
m_j \geq m_4 \quad (j = 1, 2, 3),
\]

(5.13)
which guarantees the positive value of the flow rate $Q_{j}^{I-SMB}$ ($j = 1, 2, 3$).

**Cost function**

From the economical point of view, the process performance indicators, the productivity $Pr$ and the solvent consumption $SC$, can be defined as follows:

\[
P_{r}^{SMB} = \frac{Q_{F} (Y_{A} c_{E,A} + Y_{B} c_{E,B})}{\sum n_{j} V},
\]

\[
P_{r}^{I-SMB} = \alpha Q_{F} (Y_{A} c_{E,A} + Y_{B} c_{E,B}) \sum n_{j} V,
\]

\[
SC = \frac{(Q_{D} + Q_{F})(c_{E,A} + c_{E,B})}{Q_{F} (Y_{A} c_{E,A} + Y_{B} c_{E,B})}.
\]

(5.14) (5.15)

where $Y_{A} = Q_{E} c_{E,A} / Q_{F} c_{E,A}$ and $Y_{B} = Q_{RCR,B} / Q_{FCR,B}$ are the yield of extract and raffinate product, respectively.

In this study, fixed switch time condition and fixed $(m_{1}, m_{4})$ values, i.e. fixed $Q_{1}$ and $Q_{4}$, are applied to both conventional SMB and I-SMB operation, and assuming the separation of racemic mixture of chiral compounds, i.e. $c_{F,A} = c_{F,B} = c_{T}^{*}/2$, the required purity of each product stream is supposed to be in the same level, i.e. $X_{A,min} = X_{B,min} = X_{min}$. By considering the process mass-balance under the cyclic-steady state taking into account the conditions on the feed concentration of each component and the required product specifications, Eqs. 5.14 and 5.15
5.2 Cycle to cycle control of the I-SMB process

can be recast in the following form:

$$p_{r_{\text{SMB}}} = \frac{XQ_{\text{c}}c_{\text{F}}^T}{2 \sum n_j V}, \quad p_{r_{\text{I-SMB}}} = \frac{\alpha XQ_{\text{c}}c_{\text{F}}^T}{2 \sum n_j V},$$

$$SC = \frac{2 (Q_D + Q_F)}{XQ_F},$$

and in terms of the flow rate ratios:

$$p_{r_{\text{SMB,I-SMB}}} = \frac{Xc_{\text{F}}^T(m_3 - m_2)(1 - \epsilon^*)}{2 \sum n_j t^*},$$

$$SC = \frac{2 (m_1 - m_4 + m_3 - m_2)}{X(m_3 - m_2)}.$$

It is obvious from Eqs. 5.16 and 5.17 that the performance of the unit can be improved by increasing the feed flow rate $Q_F$ and by decreasing the desorbent flow rate $Q_D$. In order to achieve higher productivity and lower solvent consumption while fulfilling the required process constraints, the following can be the cost function of the optimization problem:

$$\min_{Q_2, Q_3, s} [\lambda_D Q_D - \lambda_F Q_F + \lambda_s \cdot s],$$

where the weights $\lambda_D$, $\lambda_F$ and $\lambda_s$ reflect the relative importance given to the different terms of the cost function, and $s$ is the vector of the slack variables. The problem described here is solved with the help of the LP solver named SeDuMi which has been developed at Computational Optimization Research at Lehigh (COR@L) [49].
5.3 Results and discussion

In this section the on-line optimizing control of the I-SMB process is demonstrated through simulations using a virtual plant, and the results are analyzed in the frame of Triangle Theory.

As a model system, the separation of the racemic mixture of Tröger’s base enantiomers, $(\pm)$-2,8-dimethyl-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine, on Chiralpak AD stationary phases and using ethanol as mobile phase, is considered. I-SMB as well as standard SMB separation of the compound has been studied in Chapter 3 and 4 [29, 40] and the adsorption behavior of the system is described by the bi-Langmuir adsorption isotherm given in Table 4.1.

The virtual plant consists of four columns in 1-1-1-1 configuration or six columns in 1-2-2-1 configuration and is operated in two different modes, i.e. I-SMB and conventional SMB. The chromatographic model used in the simulation is the same one discussed in Chapter 3 and 4 [29, 40], which is summarized in Table 4.1. All parameters in the model and the column characteristics are given in Table 3.1.

In Table 5.1, the information supplied to the controller is presented. Note that the controller only knows overall Henry’s constants of the two species, i.e. $H_i = a_{i,1} + a_{i,2}$ ($i = A,B$), as the adsorption parameters.

Theoretically, in order to achieve the complete separation of the two species the four flow rate ratios can be chosen based on the design criteria namely Triangle Theory. In the linear case for both the conventional SMB and the I-SMB process the same explicit inequalities Eq. 5.3 define the complete separation region in the operating parameter space, i.e, in the $(m_2, m_3)$ and $(m_1, m_4)$ plane [19]. For the conventional SMB separation of the compound subject to nonlinear isotherm still the equations
5.3 Results and discussion

Table 5.1: Parameters for the on-line optimizing control.

<table>
<thead>
<tr>
<th>Geometric conditions</th>
<th>Configuration 1-2-2-1</th>
<th>1-1-1-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Column geometry</td>
<td></td>
<td>S, L, e*</td>
</tr>
<tr>
<td>Henry’s constants</td>
<td>H_A</td>
<td>4.976</td>
</tr>
<tr>
<td></td>
<td>H_B</td>
<td>1.864</td>
</tr>
<tr>
<td>Constraints</td>
<td>p_{total,max} [bar]</td>
<td>40.0</td>
</tr>
<tr>
<td></td>
<td>X_A,min [-]</td>
<td>0.999</td>
</tr>
<tr>
<td></td>
<td>X_B,min [-]</td>
<td>0.999</td>
</tr>
<tr>
<td>Operating conditions</td>
<td>Fixed t’ [min]</td>
<td>6.3</td>
</tr>
<tr>
<td></td>
<td>Fixed (m_1, m_4)</td>
<td>(5.971, 1.222)</td>
</tr>
<tr>
<td></td>
<td>Initial (m_2, m_3)</td>
<td>(1.614, 5.226)</td>
</tr>
</tbody>
</table>

describing the region for the complete separation can be derived, which depend on the feed concentration and the adsorption isotherm parameters. On the other hand, in case of the nonlinear I-SMB separation no criteria for the choice of the flow rate ratios have been theoretically derived yet. It has been shown through the comprehensive simulation study that the same boundaries for the conventional SMB process can be applied [29, 40]. In Fig. 4.1 for the system of Tröger’s base enantiomers studied in this work the change of the complete separation region depending on the total concentration of the feed racemic mixture is represented. As the feed concentration increases the region is no longer the right triangle of the linear case but gets more and more distorted. Obviously from Eqs. 5.18 and 5.19, when applying fixed (m_1, m_4) condition the choice of (m_2, m_3) at the tip of the triangle, which maximizes m_3 – m_2, can lead the highest productivity and the lowest solvent consumption maintaining the complete separation. Therefore, the task of the controller can be understood as to find the optimal operating point in the (m_2, m_3) plane, i.e. the tip of the triangle, starting from a cer-
tain initial operating point without any prior information of the system nonlinearity, i.e. without knowing the exact shape of the triangle.

In a practical sense degradation of the product purity can be observed in case of the operation under the points around the ideal complete separation boundaries which are predicted by Triangle Theory, and the actual region in which the complete separation can be achieved, i.e. the real complete separation region, is narrower than the ideal region. Such real complete separation region for the system of the Tröger’s base enantiomers at various feed concentrations has been analyzed in Chapter 3 and 4 [29, 40]. At any feed concentration for six-column conventional SMB and I-SMB and four-column I-SMB the real complete separation region is almost identical to the ideal one, while the real complete separation region for the four column conventional SMB is much smaller than the ideal region. In the latter case the controller should finally find the tip of the real complete separation region in order to satisfy the required products purity.

In Fig. 5.3 and 5.4, for all four operating modes considered in this study, i.e. four and six-column conventional SMB and I-SMB, the trajectories of operating points during the optimizing control operation are shown. Fig. 5.3 represents the results of the separation at rather low total feed concentration of 1 g/L and Fig. 5.4 represents the results at 15 g/L feed concentration in which the system clearly shows the nonlinearity. In each figure, the linear triangle which is initially supplied to the controller is indicate by dotted line, and the nonlinear complete separation region in terms of the bi-Langmuir isotherm parameters and the feed concentration is indicated by solid line.

All operations have been carried out with initially clean columns and from the initial operating point as given in Table 5.1 (upper left point in each figure). As expected, for the six-column conventional SMB and
Figure 5.3: Trajectory of operating points during the optimizing control of SMB/I-SMB process. Feed concentration: 1.0 g/L. (a) Conventional SMB 1-2-2-1, (b) conventional SMB 1-1-1-1, (c) I-SMB 1-2-2-1, (d) I-SMB 1-1-1-1. Grey colored symbol: final ($m_2, m_3$). Solid line: complete separation region estimated with bi-Langmuir isotherms, dotted line: linear triangle.
Figure 5.4: Trajectory of operating points during the optimizing control of SMB/I-SMB process. Feed concentration: 15.0 g/L. (a) Conventional SMB 1-2-2-1, (b) conventional SMB 1-1-1-1, (c) I-SMB 1-2-2-1, (d) I-SMB 1-1-1-1. Grey colored symbol: final ($m_2$, $m_3$). Solid line: complete separation region estimated with bi-Langmuir isotherms, dotted line: linear triangle.
for the four-column I-SMB (subfigures (a), (c) and (d) in each figure) the controller reach the tip of the *ideal* complete separation region, and for the four column conventional SMB (subfigure (b) in each figure) the operating point moves further inside the *ideal* complete separation region, i.e. towards the tip of the *real* complete separation region. It is worth emphasizing here again that the controller has no information about what adsorption isotherm the species to be separated is subject to. Even more impressively only the simplified model of the conventional SMB is implemented in the controller. Based on the feedback information from the plant, i.e. the product purities, and on the embedded simplified model of the conventional SMB and on the optimization problem the controller is able to decide how to correct the operating conditions for the conventional SMB as well as the I-SMB separation.

Figs. 5.5 and 5.6 show the evolution of the product purities of the unit with respect to time. In all eight cases, i.e. four- and six-column conventional SMB and I-SMB at 1 and 15 g/L feed concentration, the required purity specifications of 99.9 % are fulfilled for both the extract (solid line) and raffinate (dashed lines). The improvements of the productivity during the optimization are also presented in the figures (dot-dashed line labeled $Pr$). As one can see in Eqs. 5.18 and 5.19, the final value of the productivity depends on total feed concentration, the final position of the operating parameters ($m_2, m_3$) and the unit configuration, i.e. number of columns in the unit. At the certain condition of feed concentration, the use of lower number of columns and the operation under the point farther from the diagonal line in the parameter space leads higher productivity of the process. The productivity achieved in the four column processes is better than that of the six-column processes, and when taking into account the purity constraints, finally the four column I-SMB provides better productivity than four column conventional...
5. I-SMB chromatography: On-line optimizing control

Figure 5.5: Change of Extract and Raffinate product purities and productivity during the optimizing control of SMB/I-SMB process. Feed concentration: 1.0 g/L. (a) Conventional SMB 1-2-2-1, (b) conventional SMB 1-1-1-1, (c) I-SMB 1-2-2-1, (d) I-SMB 1-1-1-1. Solid line: Extract, dashed line: Raffinate, dotted line: products specification \( (X_{A,\text{min}}, X_{B,\text{min}} = 0.999) \), dot-dashed thick line: productivity \( (Pr) \).

SMB since the latter can deliver the products fulfilling the specifications only under the operating point inside the complete separation region.

The analysis and results presented here prove that the existing optimizing controller for the conventional SMB process is able to control and optimize the I-SMB operation as well even where the compound is clearly subject to a nonlinear adsorption isotherm. Emphasizing the favorable feature of the I-SMB operation in a four-column 1-1-1-1 con-
Figure 5.6: Change of Extract and Raffinate product purities and productivity during the optimizing control of SMB/I-SMB process. Feed concentration: 15.0 g/L. (a) Conventional SMB 1-2-2-1, (b) conventional SMB 1-1-1-1, (c) I-SMB 1-2-2-1, (d) I-SMB 1-1-1-1. Solid line: Extract, dashed line: Raffinate, dotted line: products specification \((X_{A,min}, X_{B,min} = 0.999)\), dot-dashed thick line: productivity (Pr).

figuration, i.e. the same purity levels can be attained at very similar operating conditions but with four columns instead of six, the use of the optimizing controller in the I-SMB process promises to exploit its superior economic potential.
Acknowledgments

The controller discussed here has been developed in Automatic Control Laboratory at ETH Zurich (Prof. Manfred Morari). The author would like to thank Dr. Cristian Grossmann for his support on the implementation of the controller.

Nomenclature

\( a_{i,k}, b_{i,k} \): parameters in bi-Langmuir isotherm for component \( i \)
\( c_i \): fluid phase concentration of component \( i \)
\( c^T_F \): total feed concentration
\( c_{p,i} \): concentration of component \( i \) at port \( P \)
\( \bar{c}_{p,i} \): average concentration of component \( i \) at port \( P \)
\( D_i \): axial dispersion coefficient of component \( i \)
\( H_i \): Henry’s constant of component \( i \)
\( k_{s,i}a_v \): product of mass transfer coefficient and specific surface of component \( i \)
\( L \): column length
\( m_j \): flow rate ratio in section \( j \) of conventional SMB and I-SMB
\( n'_i \): adsorbed phase concentration of component \( i \) in equilibrium with the mobile phase
\( n_j \): number of the columns in section \( j \)
\( Pr \): productivity
\( \Delta P \): pressure drop
\( Q_j \): volumetric flow rate in section \( j \)
\( \hat{Q}_j \): average volumetric flow rate in section \( j \)
\( Q_P \): volumetric flow rate at port \( P \)
\( s_k \): slack variables
5.3 Results and discussion

$S$ column cross-section

$SC$ dimensionless solvent consumption

$t$ time

$t^*$ switch time

$u$ superficial velocity

$V$ column volume

$X_i$ product purity

$Y_i$ recovery of component $i$

**Greek letters**

$\alpha$ step ratio of I-SMB

$\epsilon^*$ overall bed void fraction

$\epsilon_b$ inter particle void fraction

$\lambda$ weights in objective function

$\phi$ pressure drop factor

**Subscripts and superscripts**

$A$ component $A$

$B$ component $B$

$i$ component index

$j$ section index

SMB conventional SMB

I-SMB I-SMB
5. I-SMB chromatography: On-line optimizing control
Chapter 6

Concluding remarks

This thesis presents the principles of the Intermittent SMB (I-SMB) technology, one of the modifications of the standard SMB process, analyzes for the first time its behavior and demonstrates its performance experimentally as well as through detailed simulations.

Chapter 2 presents the I-SMB process, and analyzes it based on the equilibrium theory of chromatography. In the first part of the chapter, the well known design criteria as developed for the conventional SMB, i.e. Triangle Theory, is extended to the I-SMB process under the linear chromatographic conditions. And at the same time one of the options to determine I-SMB operating parameters is introduced, i.e. the minimum switch time design. Since the I-SMB has six degrees of freedom, namely the four flow rates, the switch time and the duration of the first sub-interval, to calculate these operating parameters the four flow rate ratios that are chosen accordingly as well as two additional constraints regarding the total pressure drop of the unit are enforced.
6. Concluding remarks

It is worth noting that the I-SMB and the conventional SMB processes can be conveniently compared on the same basis by considering the corresponding flow rate ratios when applying the same pressure drop constraints in designing both processes. In the second part of the chapter, the cyclic-steady state performance of the conventional SMB and of the I-SMB processes are analyzed using the equilibrium theory model of chromatography. The analysis reveals why and how the combination of the synchronous partial feed and withdrawal operations implemented can improve the separation efficiency as compared to the conventional SMB process.

The theoretical findings discussed in Chapter 2 are assessed by experiments and detail simulations. Considering as a model system the separation of Tröger’s base enantiomers, (±)-2,8-dimethyl-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine, on Chipalpak AD stationary phases in ethanol, four different modes of operation, i.e. the conventional SMB and the I-SMB processes each operated in a six column 1-2-2-1 configuration and in a four column 1-1-1-1 configuration, have been demonstrated and their performance in terms of the product purities, the productivity and the solvent consumption are compared. The competitive adsorption behavior of the Tröger’s base enantiomers’ system has been preliminary estimated and it can be described accurately enough by the bi-Langmuir isotherm. Chapter 3 represents the separation results at a rather low total feed concentration where the system exhibits mild nonlinearity, and Chapter 4 shows the results at higher feed concentrations where the system is clearly subject to the nonlinear adsorption isotherm. Comprehensive simulation study proves that nonlinear Triangle Theory for conventional SMB separations can be applied also to I-SMB processes operated under nonlinear chromatographic conditions and that the same purity performance can be achieved in a four-column
I-SMB unit as in a six-column SMB or I-SMB unit, thus leading to higher productivity. In order to confirm the conclusions of the simulation study, experiments have been carried out. At feed mixtures of 1 g/L and 5 g/L all four operating modes considered so far have been tested. As expected, the four-column I-SMB process outperformed the six-column conventional SMB and I-SMB, i.e., the four column I-SMB doubles the productivity of the six column processes achieving the same solvent consumption. Moreover the four-column I-SMB can be successfully operated at even higher feed concentrations, 10 g/L and 15 g/L, maintaining very high product purities, i.e. 99.5%.

On the other hand, in Chapter 5, on-line optimizing control of the I-SMB process is demonstrated through simulations using a virtual I-SMB unit in order to exploit full economic potential of the process. Even at high feed concentration, i.e. under nonlinear conditions, and without any prior knowledge of the system nonlinearity, the existing controller developed for the conventional SMB unit can successfully control the I-SMB as well and optimizes the performance of the unit while delivering the products which fulfill the purity specifications and satisfying all the required process constraints.

Thus summarizing, this thesis convincingly demonstrated that I-SMB gives the opportunity to carry out a continuous chromatographic binary separation under isocratic conditions in four columns only, with high purity and high productivity, which is a big advantage particularly for cases where the stationary phase is very expensive as it is certainly the case in chiral separations. This positive feature comes with a rather simple implementation, both at the small and at the large scale, and with simple criteria for the design: operating an I-SMB unit and designing and running an I-SMB separation is as easy as an SMB separation.

The impact of partial feed and withdrawal operations on the SMB per-
formance has been discussed in previous publications [26–28]. Nevertheless, I believe that the I-SMB technology is simpler to implement, from both a theoretical and a practical point of view, and more effective. Although the I-SMB process has so far been applied to separations in the sugar industry, where adsorption isotherms are rather linear, the deployment of the I-SMB technology for difficult separations, such as that of the enantiomers of a chiral compound in the case of low selectivity, where the systems of interest are subject to nonlinear adsorption isotherms, can be a major breakthrough in preparative multi-column continuous chromatography. Only few examples of such I-SMB separations have been reported, e.g. the very first one is a separation of a pharmaceutically relevant compound, (RS,RS)-2-(2,4-difluorophenyl)butane-1,2,3-triol, an important intermediate in the production of different antifungal drugs. [41]. Because of its superior performance in the economical aspect as compared to the standard SMB, the broader application of the I-SMB in a production context will become more attractive in spite of the patent issues which should be overcome with the Japanese company [13].

Furthermore, there has been a strong indication of another great potential of the I-SMB technology, i.e. application to the three fraction separation. Note again that the I-SMB is based on a concept of partial feed and partial withdrawal, which is indeed at the heart some of the techniques used for multi-fraction separations. Recently the pharmaceutical industry has increased their interest on the three fraction separation using multi-column chromatographic processes, which can offer the access to a single pure substance in the mixture consisting of more than three components. Especially in the purification of bio-related products such as proteins and peptides, separations based on chromatography are essential because complexity of the system pre-
vents the use of other techniques such as crystallization. In the last
decade, there has been proposed several methods for the three fraction
separation, the so-called Multi-Column Solvent Gradient Purification
(MCSGP) process [50–53], and the hybrid of semi-continuous two-zone
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the same principles as I-SMB, i.e. derivation of the standard SMB pro-
cess implementing partial feed and partial withdrawal operations.

Such processes are intrinsically more complicated than SMB, but also
more flexible and more diverse. Therefore, one can expect to identify
interesting ternary separation schemes based on an evolution of the I-
SMB technique. Our next research interest is focused on this challenge.
Following the approach of intermittent feed and withdrawal strategy,
we have developed new multi-column process schemes and experiment-
tally implemented one of them on our laboratory separation unit [58].
Based on the equilibrium theory and extending the concept of Triangle
Theory as discussed in Chapter 2, one can obtain the constraints for
complete ternary separation. And to demonstrate its performance a
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Although the ternary separation technique is state-of-the-art, the cyclic-
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5.1 Parameters for the on-line optimizing control.
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