Control of simulated moving beds and advanced multi-column processes for chiral separations

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CONTROL OF SIMULATED MOVING BEDS
AND ADVANCED MULTI-COLUMN PROCESSES
FOR CHIRAL SEPARATIONS

Dissertation submitted to the

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for the degree of

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presented by

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Zurich, February 2010

Christian Langel
Wer glaubt etwas zu sein, hat aufgehört etwas zu werden
Sokrates
Abstract

The production of single enantiomer drugs requires advanced separation techniques to meet the strict regulations on the purity requirements dictated by regulatory agencies such as the Food and Drug Administration (FDA) and the European Medicines Agency (EMEA). Over the last years, multi-column chromatographic processes, like simulated moving bed (SMB), have become a well-established technique for the separation of fine chemicals and production of single enantiomer drugs. This is especially true for the purification of species characterized by low selectivities, i.e., difficult to separate, such as chiral molecules for single enantiomer drug development. There are two striking advantages of the SMB technology. Firstly, compared to batch chromatography, it has a higher productivity and lower solvent consumption, which results in lower production costs. Secondly, and even more important in pharmaceutical industry, SMB separation processes can be rapidly and reliably scaled up from drug development to industrial production scale, a very important feature in an industry where time to market is very crucial. However, when operating small scale SMB units the extra-column dead volume might become comparable to the column volume and one has to consider its effect on the separation performance of the unit.

This thesis presents guidelines and rules to calculate the extra-column dead volume for the different sections of an SMB unit and it is demonstrated how to account for it in the calculation of the operating parameters. The rules are validated through detailed simulations and experiments, separating a racemic mixture of an Allene into its pure enantiomers.

In production scale SMB units the effect of extra-column dead volume can be neglected. Nevertheless, the full exploitation of the economic advantages of SMB units is still an open issue due to the uncertainties about the physical properties of the mixture to be separated. Therefore, in operational practice, SMB units are most often operated conservatively to guarantee the purity specifications enforced by the regulatory agencies.
To address this issue different control schemes have been proposed in literature but in general the presented concepts depend on the availability of accurate physical data about the mixture to be separated, i.e. the complete adsorption isotherm. Obtaining these data can be a time consuming task which is in conflict with realizing a short time to market. This limitation was overcome by the ‘cycle to cycle’ control concept developed at ETH Zurich, which requires only minimal information about the system to be separated, namely the Henry constants of the compound to be separated and the average overall void fraction of the columns installed in the SMB unit. The proposed control concept is based on linear model predictive control (MPC) and was implemented experimentally for the separation of guaifenesin enantiomers making use of optical detectors, i.e. polarimeter, UV detector, to determine the feedback information required by the controller. The performance of the controller depends directly on the accuracy of the feedback information from the plant and it was found that the measurements of the polarimeter are greatly affected by pressure fluctuations in the measuring cell and by impurities in the system. Therefore, one of the aims of this thesis was to develop a new automated on-line HPLC monitoring system for chiral separations that overcomes the limitations of the old one. The performance of the new monitoring system was successfully tested for the separation of a racemic mixture of guaifenesin enantiomers at low feed concentrations. In a next step for the first time the ‘cycle to cycle’ optimizing controller was experimentally applied for a nonlinear chiral separation of guaifenesin enantiomers, i.e. at high feed concentrations. To benchmark the performance of our controller various case studies were carried out ranging from pump disturbances to changes in the feed mixture during an ongoing separation experiment. The experimental results clearly validate the most valuable asset of the ‘cycle to cycle’ controller: the controller can meet the product specifications and improve the separation performance with the knowledge of the linear adsorption behavior only, even if the separation at stake is governed by an unknown nonlinear adsorption isotherm. This is an important achievement since it is well known that the productivity of an SMB unit increases with the total feed concentration and therefore, this
regime is the most interesting one for industry, particularly for pharmaceutical applications and chiral separations. Moreover, the time consuming task of determining the complete adsorption isotherm for a new separation problem becomes unnecessary which helps to realize a short time to market. The ‘cycle to cycle’ controller together with the new automated on-line HPLC monitoring system offer a fast and reliable way to set up new chiral SMB separation. To demonstrate this important feature of our control concept the separation of a new compound was carried out, namely the separation of Troeger’s Base enantiomers on the stationary phase CHIRALPAK™ AD using pure ethanol as mobile phase. It is shown that the proposed control concept is simple enough to be implemented quickly and reliably for a new separation campaign.

Another direction in the research field of advanced multi-column chromatographic processes aims at developing modified SMB schemes to improve the separation performance yet guaranteeing the specified purity specifications. One of these modifications is presented in this thesis, the intermittent simulated moving bed (I-SMB) process. This process is based on intermittent feed and product withdrawal and was first patented by the Nippon Rensui company under the name improved SMB (ISMB) process. This thesis presents the principle of the I-SMB process, the design criteria in the frame of the triangle theory, and the successful experimental implementation for the separation of the chiral compound (RS,RS)-2-(2,4-difluorophenyl)butane-1,2,3-triol, an important intermediate in the production of different antifungal drugs.
Zusammenfassung


In grösseren SMB-Anlagen, wie sie für die Produktionsphase verwendet werden, kann der Effekt des Totvolumens auf die Trennleistung vernachlässigt werden. Trotzdem ist die volle Ausnutzung der wirtschaftlichen Vorteile welche
die SMB Technologie bietet aufgrund der Unsicherheiten bei der Bestimmung der physikalischen Eigenschaften der zu trennenden Mischung immer noch schwierig. Aus diesem Grund werden SMB-Anlagen in der Regel unter konservativen Betriebsbedingungen gefahren um die Produktspezifikationen, die von den Regulierungsbehörden verlangt werden, zu gewährleisten.


Ein Ziel dieser Arbeit war es, ein neues automatisches online Überwachungssystem zu entwickeln, welches auf Hochleistungsflüssigkeitschromatographie (HPLC) basiert und in der Lage ist, die "feedback information" für den Regler präzise und zuverlässig zu bestimmen und damit die Grenzen des alten Systems überwindet. Die Leistungsfähigkeit des neuen online HPLC Überwachungssystems wurde experimentell getestet indem die Trennung

Eine andere Richtung im Bereich der Forschung über Mehr-Kolonnen chromatographischer Trennprozesse zielt darauf ab, neue Prozesse zu entwickeln,
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Chapter 1

Introduction

The Simulated Moving Bed (SMB) technology was invented and introduced to industry in the early 60’s of the last century by Gerold and Broughton from Universal Oil Products (UOP) (Broughton and Gerold, 1961). The process was developed for large scale separations of petrochemicals, which were difficult to carry out using conventional separation techniques such as distillation. In the following years more than 130 production units were licensed by UOP (Ruthven and Ching, 1989). However, it took until the early 1990s before SMB technology was first applied to other systems, such as the separation of enantiomers (Negawa and Shoji, 1992; Ching et al., 1993; Nicoud et al., 1993). The practitioners soon realized the great potential of SMB for enantiomeric separations and in 1997 UCB Pharma installed a multi-ton large scale SMB separation unit (McCoy, 2000). In 2002, a further breakthrough was achieved when the US Food and Drug Administration (FDA) approved the production of the first single enantiomer drug, Lexapro from Lundbeck, using SMB technology (Anon., 2003). The market for single enantiomer drugs in pharmaceutical industry has gained more and more competitiveness for a good reason: many of the so-called block buster drugs, generating more than
1 billion dollar revenue a year, are enantiomerically pure drugs. Therefore, in this industry time to market is of great importance and the economics of the actual separation are of minor interest (Francotte and Richert, 1997). As a matter of fact, SMB technology is now a well established technique in the separation of fine chemicals and in the production of single enantiomer drugs and SMB units have been installed in various pharmaceutical companies to support drug development, e.g. Bayer, Carbogen, GlaxoSmithKline, Merck, Novartis, Novasep, Pfizer, and Pharmacia. Commercial scale systems are operated at Aerojet, Finorga, H. Lundbeck, Honeywell, UCB Pharma. The largest units that are currently operated process up to 200 metric tons of material per year (Anon., 2003).

There are two striking advantages of the SMB technology. Firstly, compared to batch chromatography, it has a higher productivity and lower solvent consumption, which results in lower production costs. Secondly, and even more important in pharmaceutical industry, SMB separation processes can be rapidly and reliably scaled up from drug development to industrial production scale, and therefore they enable a shorter time to market. The scaling is so easy since the same stationary and mobile phases used in the development phase, where only a few grams of product are required, can be as well used in the production phase. These economic advantages have firmly established SMB in recent years as the state-of-the-art technology for complex separation tasks in the areas of pharmaceuticals, fine chemicals and biotechnology, especially for the purification of species characterized by low selectivities, i.e. difficult to separate, such as chiral molecules for single enantiomer drug development (Juza et al., 2000).

Nevertheless, the full exploitation of the economic advantages of SMB has been hindered mainly by two factors. On the one hand, the uncertainty in the physical properties of the mixture, i.e. the adsorption behavior, limits the optimal design and operation of the SMB separations. On the other hand, regulatory agencies like the Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) dictate increasingly stricter regulations
and harder constraints on the purity and quality of chiral drugs. These requirements enforce the selection of operating conditions that will guarantee the fulfillment of the purity specifications in the face of these uncertainties. Eventually, these regulations translate into conservative operation conditions to guarantee the necessary robustness, at the price of sacrificing productivity. Thus, the regulatory issues on top of the lack of accurate data about the mixture lead to a considerable loss of productivity in industrial SMB applications.

The application of a suitable controller could allow to tackle these issues by optimizing the operating conditions to exploit the full economical potential of the SMB concept for given product specifications. Different control schemes were proposed in literature, but in general the bottleneck of these approaches is the need for accurate adsorption data of the system to be separated (Kloppenburg and Gilles, 1999a; Klatt et al., 2000, 2002; Wang et al., 2003; Schramm et al., 2003a; Toumi and Engell, 2004; Song et al., 2006c,a,b; Engell, 2007). However, it is well known that the determination of the adsorption behavior is by itself a very difficult and time-consuming task.

In the SMB control group at ETH Zurich a control scheme was presented that requires only minimal information about the system to be separated, namely the Henry's constants of the compounds to be separated and the average overall void fraction of the columns installed in the SMB unit. The controller is based on model predictive control (MPC) and guarantees the fulfillment of the process specifications (maximum allowable pressure drop, product purities), while optimizing at the same time the process performance. In the past years the controller was validated experimentally and through simulations for achiral and chiral separations (Abel et al., 2004a; Erdem et al., 2004a,b; Abel et al., 2005; Erdem et al., 2005, 2006). In this control scheme the information about the concentration levels of both components in the raffinate and extract stream was fed back to the controller with a relatively high frequency, i.e. every five seconds. As a next development step, the so called 'cycle to cycle' controller was presented, which uses the concentration of two components in both product streams averaged over one cycle as feedback information (Grossmann
et al., 2008b), i.e. feedback frequency once per cycle. The proposed ‘cycle to cycle’ controller was applied experimentally making use of a combination of two on-line optical detectors, i.e. UV and polarimeter, to determine the feedback information (Amanullah et al., 2007). It was found that the accuracy of the polarimeter is greatly affected by experimental disturbances, such as pressure fluctuations in the measuring cell or impurities in the system, which is a problem since the performance of the controller depends directly on the accuracy and reliability of the feedback information from the plant. One of the objectives of this thesis was to design and implement a new monitoring system for chiral separations that overcomes the limitations imposed by the old monitoring device, and that allows also to monitor the concentrations in the two product streams even if the plant is operated at high feed concentrations.

Another direction in the research field of SMB technology aims at developing modified SMB schemes to improve the separation performance. In particular one can distinguish two different approaches, namely development of new multi-column process schemes or modifications in the operation mode of the conventional SMB. For the latter category different concepts were proposed and examples among these are PowerFeed where the feed flow rate is varied within a switch (Zhang et al., 2003, 2004), ModiCon where the feed concentration is modulated within a switch period (Schramm et al., 2002, 2003c,b), solvent gradient simulated moving bed operation (Antos and Seidel-Morgenstern, 2001, 2002; Abel et al., 2002, 2004c), and the EE-SMB enriched extract SMB where part of the extract stream is continuously concentrated before being re-injected to Section 2 of the SMB (Bailly et al., 2004; Paredes et al., 2006).

However, instead of modifying the operation mode, different groups have proposed new process schemes for multi-column chromatographic processes that allow to increase the feed throughput per volume of stationary phase material. These systems are of special interest for chiral separations since the costs for the stationary phase material account for a huge part of the total production costs. The concept of partial feed and partial withdrawal allows to change the internal flow rates during the switch period and the idea was first presented
1.1 Enantiomers and their relevance in pharmaceutical industry

Enantiomers are stereoisomers that are mirror images of each other and cannot be superimposed. They behave like one’s left and right hand and are referred to as chiral compounds. The most common reason for chirality in nature is the presence of an asymmetric carbon atom, i.e. an atom that is attached to four different groups or atoms. Enantiomers exhibit identical physical and chemical properties and can only be distinguished upon their ability to rotate polarized light in equal amounts but opposite directions. A mixture containing 50% of each enantiomer is called racemic and will have a net rotation of zero, when exposed to polarized light. Several chiral amino acids are present in living organisms that show different behavior when reacting with other molecules that are also chiral. There can be a huge difference in the effects that two enantiomers can cause in a living organism. This is of special interest for the pharmaceutical industry when drugs are administered in their racemic form.
1. Introduction

In this case there are two possible scenarios: one of the two enantiomers shows the desired therapeutic effect, whereas the other one might not be active at all. In the second and more dramatic case, one enantiomer has the intended therapeutic effect, but the other one exhibits adverse effects. A tragic example of the latter case is the racemic drug Thalidomide that was administered to pregnant women in the late 1950s and early 60s. One of the enantiomers was effective against morning sickness, whereas the other one was teratogenic. Although this tragic case was known to the industry and to the public, it took until the early 90s for the regulatory agencies such as the FDA and the EMEA to enforce strict regulations on the purity specifications of chiral drugs. Since then the market share of single enantiomer drugs increased from 10% before the 1990s to about 37% in 2005. That corresponds to sales of US$225 billion in 2005 with the top three selling drugs being Lipitor (Pfizer, Astellas), Plavix (Sanofi-Aventis, Bristol-Myers Squibb), and Epogen/Procrit (Amgen, Johnson&Johnson) (Erb, 2006). Given these numbers it is rather obvious that the industry shows an increasing interest in separation techniques such as SMB chromatography which allow to separate racemic mixtures of enantiomers into their pure components.

1.2 Principle of the SMB Technology

Simulated moving bed (SMB) technology is a continuous countercurrent separation process that exploits the principles of chromatography to achieve the separation of usually two compounds contained in a mixture. Its name originates from the fact that the movement of the solid phase is mimicked by shifting the inlet and outlet ports of the unit in the direction of the fluid flow over a finite length at discrete time intervals, as illustrated in Fig. 1.1 (Mazzotti et al., 1997). The principle of the process can be best explained with reference to the true countercurrent process, the so called True Moving Bed (TMB), where the movement of solid phase is indeed real and not only simulated. The separation of the feed mixture is carried out by exploiting the different affinity
1.2 Principle of the SMB Technology

of the compounds to the stationary phase. The unit is divided into 4 sections by the different inlet and outlet ports (see Fig. 1.1): the Feed and the Desorbent enter the unit between section 2 and 3 and 4 and 1, respectively, whereas the two product streams Extract and Raffinate are withdrawn after section 1 and 3, respectively. Let us consider a mixture of two components (A and B, with B being the less retained component), which has to be separated into its corresponding pure fractions. In order to achieve complete separation, each of the different zones in the TMB has to fulfill a certain task and the ratio between the liquid and solid flow has to be chosen accordingly. The actual separation takes place in the two central sections, and the less retained component (B) is carried to the Raffinate port with the fluid flow, whereas the more retained component (A) has to be conveyed to the Extract port with the solid flow (see Fig. 1.1). In section 1 and 4 the regeneration of the stationary and the liquid phase are carried out, respectively.

In practice it is very difficult and sometimes even impossible to physically realize and implement the movement of the solid phase. In SMB technology this problem is overcome by simulating the movement of the stationary phase. An SMB unit consists of a number of columns connected in series where the inlet flows (Desorbent, Feed) and the outlet flows (Raffinate, Extract) are fed and withdrawn continuously. The period between two consecutive switches is referred to as the switch time, $t^*$. Although the countercurrent flow is only simulated the main advantages of a continuous process can still be observed. Comparing SMB to batch chromatography, lower solvent consumption and higher productivity lead to lower production costs.

The similarity between TMB and SMB can be exploited to compare the two unit operations in terms of their separation performance. This can be done by guaranteeing that the kinematic and geometric conversion rules are fulfilled (Ruthven and Ching, 1989; Storti et al., 1993), i.e.

$$\frac{V}{t^*} = \frac{Q_s}{1 - \epsilon^*} \quad (1.1)$$
\[ Q_j^{SMB} = Q_j^{TMB} + \frac{Q_s \epsilon^*}{1 - \epsilon^*} \]  

In the above equations \( V \) is the volume of the column, \( \epsilon^* = \epsilon + \epsilon_p(1 - \epsilon) \) is the overall void fraction of the column with \( \epsilon \) being the void fraction of the bed and \( \epsilon_p \) the porosity of the solid phase material; \( t^* \) is the switch time, i.e. the duration between two consecutive switches of the ports in the SMB unit, and \( Q_j^{SMB} \) and \( Q_j^{TMB} \) are the flow rates in the SMB and TMB in section \( j \) \((j = 1, ..., 4)\), respectively.

As already mentioned, the design of a successful TMB separation for a given separation problem is based on choosing the right flow ratios between the fluid and the solid flow for the different sections. The net fluid and solid flow in section \( j \) can be combined to yield a dimensionless flow rate ratio \( m_j \), which will be an important parameter in the design of the SMB separation as we will see later in Section 1.4.

\[ m_j = \frac{Q_j^{TMB} - Q_s \epsilon_p}{V(1 - \epsilon_p)}, (j = 1, ..., 4) \]  

Applying Eqs. 1.1 and 1.2, one immediately obtains the relationship for the corresponding SMB unit.

\[ m_j = \frac{Q_j^{SMB} t^* - V \epsilon^*}{V(1 - \epsilon^*)}, (j = 1, ..., 4) \]

### 1.3 Different SMB models

The mathematical model of an SMB unit consists of the material balance equations of the single columns coupled with the mass conservation equations describing the nodes. There are different degrees of complexity that an SMB model can incorporate and account for; a good overview has been reported in literature (Guiochon et al., 2006). The degree of complexity is determined by the physical accuracy of the model, i.e. a model becomes more complex if all the phenomena taking place in the system are covered. One of such
1.3 Different SMB models

Figure 1.1: Scheme of the 2-2-2-2 laboratory scale SMB plant. The dashed line indicates the possibility of an open or closed loop system.
SMB models is the so-called detailed solid-film linear driving force model. It takes into account the accumulation in the solid and in the liquid phase, it considers axial dispersion and convection in the fluid phase, and finally it also considers the kinetic effects assuming that the diffusion in the solid phase is the rate limiting step. The detailed model for a single chromatographic column consists of the following material balances together with the proper initial and Danckwerts boundary conditions (Guiochon et al., 2006):

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

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

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

where \( n_i \) and \( c_i \) are the concentration in the solid and liquid phase of component \( i \), respectively, \( u \) is the superficial velocity of the fluid, \( D_{L,i} \) is the axial dispersion coefficient of component \( i \), and \( t \) and \( z \) are the time and space coordinate, respectively. In Eq. 1.6 \( a_p \) is the specific surface of the adsorbent, \( k_i \) the overall mass transfer coefficient of component \( i \), and \( n_i^* \) is the adsorbed phase concentration in equilibrium with the fluid phase concentration \( c_i \). The Danckwerts boundary conditions read as follows:

\[
\left[ uc_i - D_{L,i} \frac{\partial c_i}{\partial t} \right]_{z=0} = u c_0,
\]

\[
\frac{\partial c_i}{\partial z} \bigg|_{z=L} = 0.
\]

The detailed model should be applied whenever the column performance is limited because of kinetic effects, however, its use requires the availability of data on mass transfer and dispersion coefficients. Moreover, the use of the detailed model can require a lot of computational power.

Van Deemter et al. demonstrated that for linear chromatography the mass transfer resistance and axial dispersion can be lumped together in an apparent axial dispersion coefficient, \( D_{ap,i} \) (Vandeemter et al., 1956). If in addition, it is
1.3 Different SMB models

enforced that the stationary and mobile phase are always in equilibrium. The obtained chromatographic model is referred to as the equilibrium dispersive model (EDM) which exhibits a good compromise between model accuracy and computational effort, i.e.

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

(1.10)

When solving this model numerically, one can further reduce the complexity of the model by setting the numerical dispersion equal to the apparent axial dispersion coefficient which is achieved by choosing the number of grid points equal to the number of theoretical stages (Migliorini et al., 1999a). In this case the right hand side of Eq. 1.10 becomes zero. This method has been used in the development of the SMB controller presented in this work. As already mentioned, this approach is exact for linear chromatography, but it has been shown that it can be extended to nonlinear chromatography without losing accuracy of the results as long as the equilibrium kinetics are not too slow, i.e. the efficiency of the columns is high enough (Migliorini et al., 1999a). The chromatographic columns used for chiral separations are very efficient with theoretical plate numbers that can easily be a few hundreds, which is well above the limitations. Therefore, the equilibrium dispersive model is widely applied to model chiral chromatographic processes.

A further simplification is the equilibrium model also referred to as ideal model, where mass transfer and dispersion effects are neglected. In this case the right hand side of Eq. 1.10 becomes zero and this model is the basis for the development of the triangle theory which is successfully applied to design SMB separations and will be discussed in the next Section.
1.4 Design of the SMB process ”Triangle Theory”

The design of an SMB separation involves the selection of five operating parameters: the switch time $t^*$, and the four flow rates in the different sections ($Q_1, ..., Q_4$). To be able to determine the five operating parameters, five constraints have to be enforced, namely the four $m_j$ values of the different sections and another constraint discussed in the following.

The chiral stationary phases used for the separation of enantiomers are typically subjected to maximum allowable pressure drop specifications, i.e. violating this limit would damage the stationary phase material and consequently lead to degradation of the separation performance. Therefore, it is common practice in the design of SMB separations to enforce that the pressure drop inside the unit fulfills the specifications throughout the whole operation. This constraint will be applied in the design of the SMB operation and the pressure drop along the column can be calculated applying Darcy’s law, i.e.

$$\frac{\Delta P_j}{L} = \phi \frac{Q_j}{S}.$$  \hspace{1cm} (1.11)

In above equation $\Delta P_j$ is the pressure drop along one column in section $j$, $L$ and $S$ are the length and the cross section of the column, and $\phi$ is a parameter depending on the stationary phase material and on the fluid phase. The total pressure drop, $\Delta P$, along the unit is obtained according to following equation:

$$\Delta P_{\text{max}} = \Delta P = \sum_{j} n_j \Delta P_j,$$ \hspace{1cm} (1.12)

where $n_j$ is the number of columns in section $j$. Selecting the four flow rate ratios for the different sections and applying Eq. 1.4 together with Eq. 1.12 one obtains the minimum switch time, $t^*$, for a given $\Delta P_{\text{max}}$, i.e.

$$t^* = \frac{\phi L^2}{\Delta P_{\text{max}}} \sum_{j=1}^{4} n_j (m_j(1 - \epsilon^*) + \epsilon^*).$$ \hspace{1cm} (1.13)
In the frame of the triangle theory it has been demonstrated that at steady state conditions the key design parameters influencing the separation performance of an SMB are the dimensionless flow rate ratios $m_j$ (Mazzotti et al., 1997; Migliorini et al., 1999a). In the following the design criteria for complete separation are presented for linear and Langmuir adsorption isotherms.

### 1.4.1 Linear isotherm

Let us first consider a separation governed by a linear adsorption isotherm:

$$n_i = H_i c_i, \quad (1.14)$$

with $H_i$, the Henry constant of component $i$. Applying equilibrium theory and writing the corresponding mass balances the following criteria for the choice of the flow rate ratios $m_j$, which if fulfilled lead to complete separation, can be derived (Mazzotti et al., 1997):

$$H_A \leq m_1,$$
$$H_B \leq m_2 \leq H_A,$$
$$H_B \leq m_3 \leq H_A,$$
$$m_4 \leq H_B. \quad (1.15)$$

The separation conditions can be graphically represented in a plane spanned by the flow rate ratios $m_2$ and $m_3$, see Fig. 1.2. Since $m_3$ is always larger than $m_2$ all feasible points will lie above the diagonal in the $(m_2, m_3)$ plane. In the linear case the triangle of complete separation is bounded by values of the Henry constants $H_A$ and $H_B$. It has been demonstrated that the productivity of an SMB separation is proportional to the distance from the diagonal (Mazzotti et al., 1997). Consequently, the vertex of the triangle of complete separation labeled as $w$ in Fig. 1.2 indicates the operating point achieving maximum possible productivity. In the regions above and to the left of the triangle of complete separation, pure Extract (E) and pure Raffinate (R) are obtained,
1. Introduction

1.4.2 Langmuir isotherm

In most cases the linear adsorption isotherm is only valid at very low feed concentrations and more complex adsorption isotherm have to be used to describe the thermodynamics of adsorption at higher feed concentrations. A large variety of nonlinear adsorption behaviors is covered by the Generalized Langmuir
isotherm which reads as follows (Mazzotti, 2006c):

\[ n_i = \frac{N_i K_i c_i}{1 + p_1 K_{A c A} + p_2 K_{B c B}}, \]  

(1.16)

where \( N_i \) and \( K_i \) are the saturation loading capacity and the equilibrium constant of component \( i \). The parameters \( p_1 \) and \( p_2 \) can take the values \( \pm 1 \), hence, four different adsorption isotherms are possible. It has been shown that in the frame of equilibrium theory exact criteria for complete separation could be derived analytically for all four cases (Mazzotti, 2006a,b). In the following, the case for \( p_1 \) and \( p_2 \) equal to +1, corresponding to the competitive Langmuir isotherm, will be discussed in more detail. The conditions of complete separation can be written as:

\[ H_A < m_1 \]  

(1.17)

\[ m_{2, \text{min}} < m_2 < m_{2, \text{max}} \]  

(1.18)

\[ m_{3, \text{min}} < m_3 < m_{3, \text{max}} \]  

(1.19)

\[ m_4 < m_{4, \text{max}} \]  

(1.20)

It should be noted that all the upper and lower bounds except for \( m_1 \) are functions of \( m_2, m_3 \), the adsorption isotherm parameters and the feed concentration. Moreover, the boundaries on \( m_1 \) and \( m_4 \) are explicit, whereas the ones on \( m_2 \) and \( m_3 \) are implicit functions. However, the constraints on the flow rate ratios in the two central sections do not depend on \( m_1 \) and \( m_4 \), hence the complete separation conditions can be graphically represented in the \((m_2, m_3)\) plane, as shown in Fig. 1.3. The complete separation region is still triangular-shaped, yet no longer regular as in the linear case, but distorted. The different separation regions for pure Raffinate, no pure stream, and pure Extract are located in the same position with respect to the complete separation region as they are in the linear case. It has to be noted that the information about the separation regions withdrawn from the \((m_2, m_3)\) plane is only valid as long as the constraints on \( m_1 \) and \( m_4 \) are fulfilled. This is true for the linear and the Langmuir case presented here as well as for the other cases of the Generalized
1.5 Structure of the thesis

The objective of this work is to develop advanced multi-column chromatographic processes for challenging separation problems as well as to design and implement a new automated online HPLC monitoring system for the ‘cycle to
1.5 Structure of the thesis

cycle' controller developed within the SMB control group at ETH Zurich. In this thesis all the separations presented are carried out for chiral compounds, but the theory and processes developed can of course also be applied to non chiral separations. The thesis is organized into eight Chapters and structured so as to follow the different steps within the research project chronologically.

Chapter 2 presents the effect of extra-column dead volume on the separation performance in small scale laboratory SMB units; in small scale SMB units the extra-column dead volume of the connecting tubing parts and the valves may become comparable to the column volume. In this case one needs to account for the extra-column dead volume in the design of the operating conditions to guarantee proper and satisfactory operating conditions. Therefore, rules and guidelines are determined to calculate the extra-column dead volume for the different sections of an SMB and to account for its effect on the separation performance. The theory is validated and supported through simulations and experiments. For the experiments a racemic mixture of (±)-3,5-bis[1-(4-methoxyphenyl)-1-methyl]hepta-3,4-diene-1,6-diynie was separated, also referred to as Allene (Livingston et al., 2001, 2002; Nielsen and Diederich, 2002; ter Wiel et al., 2007). The compound was provided to us from the Laboratory of Organic Chemistry at ETH Zurich and it has been the first time that this compound could be separated successfully for further use in the laboratory of the organic chemistry department.

Chapter 3 is devoted to present the general concept of our ‘cycle to cycle’ controller which has been developed within the SMB control group of ETH.

Chapter 4 deals with the design and the implementation of an automated online high-performance-liquid chromatography monitoring system. The monitoring system was installed to overcome the limitations associated to the former monitoring device which made use of optical detectors such as polarimeter and UV detector to extract the information about the concentration of both enantiomers in the two product streams of an SMB. This information is required as feedback information by our controller and is of great importance since the performance of the controller is directly affected by the quality and
accuracy of the feedback information from the plant. The performance of the new monitoring system is tested experimentally for the separation of Guaifenesin enantiomers at low feed concentration.

In Chapter 5 the 'cycle to cycle' controller together with the newly developed monitoring system are used for a nonlinear chiral separation of Guaifenesin enantiomers, i.e. at high feed concentrations. This is a major achievement since it is well known that the productivity of an SMB unit increases with the total feed concentration and therefore, this regime is the most interesting one for industry, particularly for pharmaceutical applications and chiral separations. Moreover, the results demonstrates that our controller is able to perform under nonlinear operating conditions although it is only based on linear information about the adsorption behavior of the components to be separated. To evaluate the performance of our controller various case studies are carried out ranging from pump disturbances to changes in the feed mixture during an ongoing separation experiment.

In a next step after having proven that the controller is able to perform under nonlinear operating conditions it should be demonstrated how much effort and which steps are required to set up the controller for a new separation problem. Chapter 6 presents the results for the separation of Troeger’s Base enantiomers. In this work the actual experimental results are compared to simulation results to understand how well the simulations can predict the dynamic and the steady state behavior of the controller.

Chapter 7 presents the intermittent simulated moving bed (I-SMB) process a modification of the conventional SMB which aims at improving the separation performance, yet guaranteeing the purity specifications. At first the principle of I-SMB is explained before discussing the process in the frame of the triangle theory and presenting the necessary steps to design an I-SMB separation. The Chapter also presents first experimental results for the I-SMB which highlight the increase in separation performance compared to a conventional SMB unit.

Finally, Chapter 8 gives a brief outlook on research activities that have already been started and will be continued in the future. The goal of the new projects
will be to develop and to implement new chromatographic process schemes that allow for three fraction separations within one process step.

Please note that the outcome and the results of this work stem from the cooperation among three different research institutes within ETH Zurich, namely the Automatic Control Laboratory (Prof. Manfred Morari, Cristian Grossmann), the Institute of Chemical and Bioengineering (Prof. Massimo Morbidelli), and the Institute of Process Engineering (Prof. Mazzotti, Shigeharu Katsuo, Mohammad Aman Ullah and me). The people listed are the ones I worked with in close collaboration but there would be more to mention which have worked in the three institutes before I joined the team. The main part of the work on developing the controller was carried out by the people of the Automatic Control Laboratory, whereas the design of the new monitoring system and the experimental implementation of the new monitoring system involved people from Institute of Process Engineering. Cristian Grossmann and I built up the monitoring system and carried out all the experiments presented in this thesis involving the controller. The work on the extra-column dead volume in small scale SMB units presented in Chapter 2 was carried out together with my colleague Shigeharu Katsuo. The same is true for the work on I-SMB and the new process schemes for multi fraction separations. Within the European project INTENANT, Daniela Acetti a PhD student from the organic chemistry department of Politecnico Milano visited us in our labs here at ETH. During this stay we separated the racemic compound (2RS,3RS)-2-(2,4-difluorophenyl)butane-1,2,3-triol, which is an important intermediate for the preparation of different types of antifungal drugs. The results of this collaboration are presented in Chapter 7.
1. Introduction
Chapter 2

Effect of extra-column dead volume in small scale SMB units

2.1 Introduction

Laboratory and small scale Simulated Moving Bed (SMB) units consist of High Performance Liquid Chromatography (HPLC) columns connected in series, where the associated extra-column dead volume connecting columns and valves may become comparable to the column volume. In these cases, the extra-column dead volume has to be taken into account in the design and simulation of SMB separations to guarantee proper and satisfactory operating conditions. This issue has been mentioned and discussed in previous works (Yun et al., 1997; Wu et al., 1998; Migliorini et al., 1999b). The effect of extra-column dead volume on the retention time of the compounds to be separated was
studied, and it was demonstrated how to account for it in the calculation of the SMB operating parameters (Migliorini et al., 1999b). Later a formula was proposed to determine the dead volume for the different sections of an existing laboratory SMB unit (Pedeferri et al., 1999; Abel et al., 2005). According to this formula, the dead volume for the different sections is obtained by dividing the overall extra-column dead volume of one section by the number of columns in this section. More recently, we have reached the conclusion that such a formula is not correct. Therefore, the objective of this chapter is to present guidelines and rules to calculate the extra-column dead volume for the different sections of an SMB unit and to discuss its effect on the separation performance.

In Section 2.3.1 a general rule to account for the extra-column dead volume is derived. In the following its effect is analyzed and discussed through simulations making use of a model that accounts for the extra-column dead volume based on the exact geometric configuration of the laboratory SMB unit. In addition, the conclusions are supported experimentally through results obtained for the separation of a racemic mixture of (±)-3,5-bis[1-(4-methoxyphenyl)-1-methyl]hepta-3,4-diene-1,6-diyne, also referred to as Allene (Livingston et al., 2001, 2002; Nielsen and Diederich, 2002; ter Wiel et al., 2007). The obtained experimental data are compared to the simulation results and the effect of extra-column dead volume on the separation is presented in the frame of the triangle theory (Mazzotti et al., 1997; Gentilini et al., 1998).

2.2 Laboratory HPLC-SMB unit

2.2.1 SMB unit

In Fig. 2.1, a schematic of our laboratory four section SMB unit in the 2-2-2-2 configuration is shown, with the inlet (Feed F, and Desorbent D) and outlet ports (Raffinate R, Extract E, and Outlet O). Note that in Fig. 2.1, the possibility of an open or closed loop system is considered. In the latter case, the stream recovered at the O port of the last column of section 4 is mixed
before the inlet of the recycling pump with fresh desorbent and fed back to the first column of section 1, whereas in the former case, the stream is completely withdrawn at the O port. In this configuration the recycling pump is not part of the SMB loop, hence the volume containing the recycling pump and the related tubing is not relevant for the dead volume considerations. However, the tubing connecting the last column of the loop to the first is indeed part of the loop, but since the pressure at the D port is larger than that at the O port there is no flow in that tubing. Our unit represents only one of the possible implementations of an SMB system, and the port configuration is one among all conceivable ones illustrated in Fig. 2.2. The two inlet and three outlet streams are not labeled explicitly, since their relative position can be chosen arbitrarily as far as the analysis below is concerned. If in the following discussion it is needed to define a certain port explicitly, the notation shown in Fig. 2.2(c) will be used. The volume of the tubing connecting an inlet port (D or F) to a column inlet is indicated as $V_{p}^{i}$ (p = D,F), whereas the one connecting the column outlet to an outlet port (E, R or O) is $V_{p}^{o}$ (p = E,R,O). The set of tubing connecting two successive columns, i.e. between the previous column’s outlet and the next column’s inlet, has the same volume $V^{D}$.

An important alternative implementation of the SMB technology is commercialized by the French company, Novasep, where the recycling pump is part of the SMB loop and its presence is compensated by an asynchronous switch of the inlet and outlet ports (Hotier and Nicoud, 1996; Hotier et al., 1996). This case is not among these considered here.

### 2.2.2 Mathematical model of the SMB unit

In this work the SMB unit is viewed as an assemble of chromatographic columns separated by pieces of tubing, according to the relevant port location, i.e. one of these in Fig. 2.2. Depending on the relevant outlet and inlet flows, the different tubing pieces experience different flow rates, which affect the residence time accordingly.
2. Effect of extra-column dead volume in small scale SMB units

Figure 2.1: Scheme of the 2-2-2-2 laboratory scale SMB unit.
2.2 Laboratory HPLC-SMB unit

(a) Outlet port

(b) Inlet port

(c) Notation

Figure 2.2: Illustration of the different possible outlet and inlet port configurations.
For the chromatographic column we use the equilibrium-dispersive model, hence the mass balance for component $i$ can be written as (Migliorini et al., 1999a,b; Guiochon, 2002; Guiochon et al., 2006):

$$
\epsilon^* \frac{\partial c_i}{\partial t} + (1 - \epsilon^*) \frac{\partial n_i^*}{\partial t} + u \frac{\partial c_i}{\partial z} = \epsilon^* D_{ap,i} \frac{\partial^2 c_i}{\partial z^2} \quad (i = A, B) \quad (2.1)
$$

The right hand side of the equation accounts for axial dispersion and mass-transfer resistance, lumped together in an apparent dispersion coefficient, $D_{ap,i}$. In Eq. 2.1, $c_i$ and $n_i^*$ are mobile phase and equilibrium stationary phase concentration, respectively. The phase equilibrium between the fluid and the adsorbed phase is characterized by the adsorption isotherm $n_i^* = f_i(c_A, c_B)$. Moreover, $\epsilon^*$ is the overall bed void fraction and $u$ is the superficial velocity of the fluid. The Danckwerts boundary conditions are implemented:

$$
\epsilon^* D_{ap,i} \frac{\partial c_i}{\partial z} \bigg|_{z=0} = u \left( c_i \bigg|_{z=0} - \phi_i^{OUT}(t) \right), \quad \frac{\partial c_i}{\partial z} \bigg|_{z=L} = 0, \quad (2.2)
$$

where $\phi_i^{OUT}(t)$ is the concentration profile at the outlet of the preceding piece of tubing.

In order to solve Eq. 2.1 numerically, the finite difference method is applied. Using a first order backward difference to discretize the first order space derivative in Eq. 2.1 leads to the following relationship:

$$
\frac{c_i(z) - c_i(z - \Delta z)}{\Delta z} = \frac{\partial c_i}{\partial z} \bigg|_z - \frac{\partial^2 c_i}{\partial z^2} \bigg|_z \frac{\Delta z}{2} + O(\Delta z^2), \quad (2.3)
$$

with $\Delta z > 0$ representing the space grid size. The numerical error introduced by neglecting the second term on the right hand side of Eq. 2.3 yields a numerical dispersion corresponding to a dispersion coefficient

$$
D_{num} = \frac{u \Delta z}{2 \epsilon^*}. \quad (2.4)
$$

Therefore, in the numerical calculations the apparent dispersion coefficients
2.2 Laboratory HPLC-SMB unit

were corrected using numerical dispersion, thus yielding

$$\bar{D}_{ap,i} = D_{ap,i} - D_{num} \quad (i = A, B). \quad (2.5)$$

The space grid size $\Delta z$ was chosen so as to fulfill the condition $\Delta z < 2\epsilon^* D_{ap,i}/u$, which depends on the superficial velocity $u$. In this work $\Delta z$ was chosen to be $L/500$ or $L/600$.

Each piece of tubing that is part of the extra-column dead volume can be described using a conventional diffusion model

$$\frac{\partial c_i}{\partial t} + u^D \frac{\partial c_i}{\partial z} = D_i^D \frac{\partial^2 c_i}{\partial z^2}. \quad (2.6)$$

In Eq. 2.6, $u^D$ and $D_i^D$ are the superficial velocity of the fluid and the dispersion coefficient of each component in the tubing, respectively. The boundary conditions for the tubing are given by

$$c_i(t, 0) = \phi_i^{IN}(t), \quad \frac{\partial c_i}{\partial z} \bigg|_{z=L^D} = 0, \quad (2.7)$$

where $\phi_i^{IN}(t)$ and $L^D$ are the concentration profile at the inlet of the tubing and the tubing length, respectively.

The variable $\phi_i^{IN}(t)$ equals $\phi_i^{OUT}(t)$ always, but in the case of the tubing immediately following Desorbent or Feed port, the following equations apply:

$$\phi_i^{IN,D}(t) = \begin{cases} \frac{Q_4}{Q_1} \phi_i^{OUT}(t) \quad &\text{closed loop,} \\ 0 \quad &\text{open loop,} \end{cases} \quad (2.8)$$

$$\phi_i^{IN,F}(t) = \frac{Q_2 \phi_i^{OUT}(t) + (Q_3 - Q_2) c_{i,F}}{Q_3},$$

where $Q_j$ is the flow rate in section $j$. The first order backward difference introduces a numerical error that can be adjusted to be proportional to the second order term on the right hand side of Eq. 2.6. Therefore, the dispersion effects in the extra-column dead volume are only described in terms of
numerical dispersion, which corresponds to saying that

\[ D_i^D = \frac{1}{2} u^D \Delta z^D, \quad (2.9) \]

with \( \Delta z^D \) being the space grid size used in the simulation. In this work a large number of grid points is desirable to minimize the effect of back-mixing in the tubing due to numerical dispersion and to focus on the role of the extra tubing in the frame of the triangle theory, i.e. the change in residence time (Migliorini et al., 1999b). Therefore, \( \Delta z^D \) was chosen as the tubing length corresponding to a volume of 0.001 mL.

The model of the SMB unit with extra-column dead volume is then formulated with the above mentioned Differential-Algebraic Equations (DAEs). The numerical solution is obtained using a DAE solver with Backward Differentiation Formula (BDF).

### 2.3 Extra-column dead volume

#### 2.3.1 Accounting for the extra-column dead volume in the frame of the ”Triangle Theory”

Comparing an SMB unit with and without extra-column dead volume, it is obvious that the extra tubing leads to an increase of the residence time of the species to be separated, as discussed earlier (Migliorini et al., 1999b).

For the sake of simplicity but without lose of generality (Migliorini et al., 1999b), let us consider two components A and B, subject to the linear isotherms

\[ n_i = H_i C_i \quad (i = A, B), \quad (2.10) \]

with \( H_A > H_B \). For any SMB operation, one can determine constraints for complete separation of the components in section 2 and 3, and regeneration
2.3 Extra-column dead volume

of the stationary and mobile phase in section 1 and 4, respectively. The con-
straints can be expressed in terms of residence time, which can be calculated
as

\[
t_{i,j}^r = t_j^D + t_{i,j}^r = \frac{V_j^D}{Q_j} + \frac{V\epsilon^*}{Q_j} \left[ 1 + \frac{(1 - \epsilon^*)}{\epsilon^*} H_i \right] (i = A,B; j = 1, \cdots, 4),
\]

(2.11)

where \( V \) is the column volume, \( V_j^D \) the dead volume that applies to section
\( j \) and will be specified later, and \( Q_j \) is the fluid flow rate in section \( j \). Equation
2.11 consists of two terms, the first being the residence time of component
\( i \) in the extra-column dead volume of section \( j \), and the second its retention
time in the chromatographic column. For complete separation, it is required
that the following constraints are fulfilled (Migliorini et al., 1999b):

\[
\begin{align*}
\text{Section 1 :} & \quad \bar{t}_{A,1}^r \leq t^* , \\
\text{Section 2 :} & \quad \bar{t}_{B,2}^r \leq t^* \leq \bar{t}_{A,2}^r , \\
\text{Section 3 :} & \quad \bar{t}_{B,3}^r \leq t^* \leq \bar{t}_{A,3}^r , \\
\text{Section 4 :} & \quad t^* \leq \bar{t}_{B,4}^r .
\end{align*}
\]

(2.12)

The effective flow rate ratio \( \bar{m}_j \) takes into account the extra-column dead
volume and is defined as follows (Migliorini et al., 1999b)

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

(2.13)

Substituting Eqs. 2.11 and 2.13 into inequalities 2.12 yields the following con-
straints on the parameters \( \bar{m}_j \):

\[
\begin{align*}
H_A & \leq \bar{m}_1 , \\
H_B & \leq \bar{m}_2 \leq H_A , \\
H_B & \leq \bar{m}_3 \leq H_A , \\
\bar{m}_4 & \leq H_B .
\end{align*}
\]

(2.14)

It is obvious from Eq. 2.13 that whenever the extra-column dead volume \( V_j^D \)
becomes very small compared to the column volume $V$ its effect can be neglected.

### 2.3.2 Calculating the extra-column dead volume

In this section, $V_j^D$ is specified for all different SMB sections as well as for all possible column configurations $(n_1-n_2-n_3-n_4)$, where $n_j$ is the number of columns in section $j$.

**Section 1** In section 1 the stationary phase needs to be regenerated completely and no A should be brought to section 4 with the next switch. Considering the case of two or more columns in section 1, as shown in Fig. 2.3(a), it can readily be seen that during the time interval between two port switches component A needs to be removed between ports $p_1$ and $p_2$ to fulfill this constraint. Therefore, the switching time $t^*$ should be larger than the residence time of the more retained component A in that section of the SMB, i.e.

$$t^* \geq t_{A,1}^j(\text{p}_1 \text{ to } \text{p}_2), \quad (2.15)$$

where $t_{i,j}^j(\text{p}_1 \text{ to } \text{p}_2)$ ($i = A,B$) is the traveling time of species $i$ from $\text{p}_1$ to $\text{p}_2$ at the flow rate prevailing in section $j$, i.e. $Q_j$. If there is only one column in section 1, as shown in Fig. 2.3(b), component A still needs to be removed between $\text{p}_1$ and $\text{p}_2$. However, the flow rate is no longer constant between $\text{p}_1$ and $\text{p}_2$ but it is $Q_1$ between $\text{p}_1$ and $\text{p}_3$ and $Q_2$ between $\text{p}_3$ and $\text{p}_2$. Hence, the requirement for complete regeneration in terms of residence time is given by

$$t^* \geq t_{A,1}^j(\text{p}_1 \text{ to } \text{p}_3) + t_{A,2}^j(\text{p}_3 \text{ to } \text{p}_2). \quad (2.16)$$

**Section 2** Fig. 2.4 illustrates the case where section 2 has two or more columns, 2.4(a), and that where it has one column only, 2.4(b). Pure A should be recovered from the Extract port, and to meet this requirement, in the
2.3 Extra-column dead volume

Figure 2.3: Scheme of section 1 for different column configurations: 2.3(a) two columns; 2.3(b) one column.
moment of the switch no B should be left in the SMB section between ports $p_1$ and $p_2$. On the other hand, to make sure that it can be obtained at the Extract port, A should not be moved beyond port $p_2$. Hence, the constraint for the switching time $t^*$ can be written as

$$t_{B,2}^*(p_1 \text{ to } p_2) \leq t^* \leq t_{A,2}^*(p_1 \text{ to } p_2).$$  \hfill (2.17)

Figure 2.4: Scheme of section 2 for different column configurations: 2.4(a) two columns; 2.4(b) one column.
Section 3  In section 3 pure B should be recovered at the Raffinate port. For the configurations where two or more columns are present in section 3, it can readily be seen from Fig. 2.5(a) that the switching time $t^*$ should be larger than the residence time of B and smaller than the one of A between ports p$_1$ and p$_2$. This leads to

$$ t_{B,3}^r(p_1 \text{ to } p_2) \leq t^* \leq t_{A,3}^r(p_1 \text{ to } p_2). $$ (2.18)

Fig. 2.5(b) illustrates the situation where section 3 consists of only one column. In order to get pure Raffinate at the Raffinate port, component A should not reach the Raffinate port hence the constraint reads as follows:

$$ t_{B,3}^r(p_1 \text{ to } p_3) \leq t^* \leq t_{A,3}^r(p_1 \text{ to } p_3). $$ (2.19)

Section 4  Operating a closed loop system, the mobile phase needs to be regenerated in section 4 to avoid pollution of section 1 with component B. Therefore, pure eluent needs to be withdrawn at the Outlet port. For the analysis of section 4 one needs to distinguish between two different possible port configurations, namely the Outlet port located after the Raffinate port or vice versa. These two configurations are shown in Figs. 2.6 and 2.7, respectively. Except for the case represented in Fig. 2.7(b), the regeneration requirement is fulfilled if the inequality

$$ t^* \leq t_{B,4}^r(p_1 \text{ to } p_2) $$ (2.20)

holds. However, with reference to Fig. 2.7(b), for the configurations containing only one column in section 4 where the Outlet port is located before the Raffinate port the residence time of the species B between p$_1$ and p$_2$ is split in two parts and the following inequality must be fulfilled

$$ t^* \leq t_{B,3}^r(p_1 \text{ to } p_3) + t_{B,4}^r(p_3 \text{ to } p_2). $$ (2.21)
2. Effect of extra-column dead volume in small scale SMB units

Figure 2.5: Scheme of section 3 for different column configurations: 2.5(a) two columns; 2.5(b) one column.
2.3 Extra-column dead volume

Summary about how to calculate the extra-column dead volume

Based on the analysis and the results above, the constraints for complete separation and regeneration can be given in terms of the effective flow rate ratios $\bar{m}_j$. The values for $V_j^D$ according to the new and the old approach can be calculated as summarized in Table 2.1. Using these values Eqs. 2.13 and 2.14 can be applied to any SMB configuration. In the case of nonlinear isotherms, it has already been shown that the constraints developed for SMB
Figure 2.7: Scheme of section 4 where the O port is positioned before the R port: 2.7(a) two columns; 2.7(b) one column.
2.3 Extra-column dead volume

units without dead volume apply, provided the effective flow rate ratios $\bar{m}_j$ are used (Migliorini et al., 1999b).
Table 2.1: Equations to calculate the extra-column dead volume for the different possible port and column configurations, for SMBs with configuration $n_1$-$n_2$-$n_3$-$n_4$.

<table>
<thead>
<tr>
<th>Dead volume</th>
<th>Port configuration</th>
<th>One column in section $j$</th>
<th>Two or more columns ($n_j \geq 2$)</th>
<th>Old approach for (Pedeferri et al., 1999; Abel et al., 2005)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_1^D$</td>
<td></td>
<td>$V_D^i + V_E^o + \frac{Q_1}{Q_2} (V_D^j - V_D^i - V_E^o)$</td>
<td>$V_D^j$</td>
<td>$\frac{(n_1 - 1)V_D^j + V_D^i + V_E^o}{n_1}$</td>
</tr>
<tr>
<td>$V_2^D$</td>
<td></td>
<td>$V_D^j$</td>
<td>$V_D^j$</td>
<td>$\frac{(n_2 + 1)V_D^j - V_F^i - V_E^o}{n_2}$</td>
</tr>
<tr>
<td>$V_3^D$</td>
<td></td>
<td>$V_F^i + V_R^o$</td>
<td>$V_D^j$</td>
<td>$\frac{(n_3 - 1)V_D^j + V_F^i + V_R^o}{n_3}$</td>
</tr>
<tr>
<td>$V_4^D$</td>
<td>O before R port</td>
<td>$V_R^i + V_O^o + \frac{Q_4}{Q_3} (V_D^j - V_R^i - V_O^o)$</td>
<td>$V_D^j$</td>
<td>$\frac{n_4V_D^j + V_O^o - V_R^o}{n_4}$</td>
</tr>
<tr>
<td></td>
<td>other cases</td>
<td>$V_D^j$</td>
<td>$V_D^j$</td>
<td></td>
</tr>
</tbody>
</table>

$V_D^j$: volume of tubing parts connecting two consecutive columns.
2.4 Experimental

2.4.1 Materials and Characterization

The chiral compound used in this study and shown in Fig. 2.8 is one of the 1,3-diethynylallenes, which are expected to be used as modules for three-dimensional acetylenic scaffolding (Livingston et al., 2001, 2002; Nielsen and Diederich, 2002; ter Wiel et al., 2007). Although these allenes are axial-chiral compounds, racemic mixtures were used for scaffolding because of the difficulties in separating the enantiomers. An access to enantiomerically pure allenes is highly desirable, and in the case of (±)-3,5-bis[1-(4-methoxyphenyl)-1-methyl]hepta-3,4-diene-1,6-diyne complete separation of the racemic mixture can be achieved on laboratory HPLC-SMB unit equipped with pre-packed CHIRALPAK™ AD columns (Chiral Technologies Europe). The stationary phase is cellulose based (amylose tris (3,5-dimethylphenylcarbamate) coated on silica support), the size of the columns is 15 cm × 0.46 cm with a particle size of 20 µm. As mobile phase, a 90/10 volume % mixture of n-hexane (Merck) and 2-propanol (Fluka) was used. All experiments were carried out at room temperature, i.e. 23±1 °C. The chromatographic analysis was per-

![Figure 2.8: Allene: (±)-3,5-bis[1-(4-methoxyphenyl)-1-methyl]hepta-3,4-diene-1,6-diyne](image_url)

formed under isocratic conditions using an HPLC system (Agilent LC System 1100 Series), which is equipped with a diode array UV detector, an automated
data acquisition system and a multi-solvent delivery system. The specification sheets of the provider (Chiral Technologies Europe) showed that in terms of retention time the columns deviate by less than 0.75% from each other. Therefore, only one column was chosen arbitrarily out of the set of available columns, and used for characterization. To determine the residence time and the overall bed void fraction of the columns, pulse injections were carried out using 1,3,5-Tris-tert-butylbenzene (TTBB) from Fluka, which is considered to be non-retained. The residence time $t_0$ was determined by correcting the retention time of TTBB with the contribution of the dead volume of the HPLC. The overall void fraction of the bed $\epsilon^*$ is calculated as

$$\epsilon^* = \frac{t_0 Q}{V}. \quad (2.22)$$

The Henry constants of the two enantiomers were determined from the retention time of the two enantiomers when performing analytical injections. The range of the linear adsorption behavior is determined by injecting solutions with increasing concentrations of the Allene, until a shift in retention time is observed. From the results of these experiments the feed concentration for the SMB runs was fixed at 0.050 g/L of racemic solution; conditions where the enantiomers are subject to the linear isotherm

$$n_i^* = H_i c_i. \quad (2.23)$$

The parameters characterizing the system are reported in Table 2.2. For numerical simulations column efficiency as a functions of fluid velocity is needed. This dependence can be expressed in terms of height equivalent to a theoretical plate (HETP) with the Van Deemter equation that for a chromatographic column operated under linear conditions, can be written as follows (LeVan et al., 1997):

$$\text{HETP}_i = \frac{2\epsilon_b D_i}{u} + \frac{2u}{(1 - \epsilon^*)^2 H_i} \left( \frac{(1 - \epsilon^*) H_i}{\epsilon^* + (1 - \epsilon^*) H_i} \right)^2 = \frac{2\epsilon^* D_{ap,i}}{u}, \quad (2.24)$$
Table 2.2: SMB, column and packing characteristics, and model parameters for the Allene enantiomers.

<table>
<thead>
<tr>
<th>Column</th>
<th>( L ) [cm]</th>
<th>( d_c ) [cm]</th>
<th>( \epsilon^* ) [-]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15</td>
<td>0.46</td>
<td>0.63</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tubing</th>
<th>( V_a ) [mL]</th>
<th>( V_b ) [mL]</th>
<th>( V_c ) [mL]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.027</td>
<td>0.023</td>
<td>0.120</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Allene</th>
<th>( H_i ) [-]</th>
<th>( k_{s,i}a_v ) [1/s]</th>
<th>( \epsilon_b D_i/u ) [cm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>3.18</td>
<td>1.83</td>
<td>( 2.21 \times 10^{-3} )</td>
</tr>
<tr>
<td>B</td>
<td>1.66</td>
<td>2.70</td>
<td>( 2.21 \times 10^{-3} )</td>
</tr>
</tbody>
</table>
where $D_i = \alpha_i u / 2 \varepsilon_b$ and $k_{s,i}a_v$ are the axial dispersion and the mass transfer coefficient of each component, respectively. In this equation, the first term on the right hand side reflects the axial dispersion in the column and the second term accounts for mass transfer; $u$ is the superficial velocity. The parameters $\varepsilon_b D_i / u$ and $k_{s,i}a_v$ can be determined by fitting Eq. 2.24 to the experimental points of HETP$_i$ vs. $u$. The HETP$_i$ can be determined for different fluid velocities under dilute conditions using the following equation (LeVan et al., 1997):

$$N_i = \frac{L}{\text{HETP}_i} = 5.54 \left( \frac{r_i^2}{W_i} \right)^2$$  (2.25)

where $N_i$ is the number of theoretical plates, $L$ the length of the column, and $W_i$ the peak width at half height. The apparent dispersion coefficient $D_{ap,i}$ to be used in Equation 2.1 can be calculated according to Eq. 2.24. This value is different for the two components and for the individual sections due to the dependence on the fluid velocity $u$.

### 2.4.2 Experimental setup

The experimental setup is based on an ÄKTA™ explorer 100 system (GE Healthcare), which was modified to fulfill our requirements (Abel et al., 2004a). Our laboratory SMB unit was set up according to the geometric configuration shown in Fig. 2.1, and has the same location of the outlet and inlet ports in each sub-unit as shown in Fig. 2.2(a), i) and 2.2(b), i). As a result, the volume of the tubing parts a, b, and c connecting the ports and the columns is the same for all sections and corresponds to the tubing, which connects the inlet port to the column inlet ($V_{ip}^1$, $p = D,F$), the column outlet to the outlet port ($V_{op}^o$, $p = E,R,O$), and the outlet port to the next inlet port ($c = V_D^D - V_p^i - V_p^o$), respectively. The volume of the different tubing parts, $V_a$, $V_b$ and $V_c$, was determined by measuring the retention time of an injected pulse of TBB (see Table 2.2). The ports connect the columns to the multi-position valves which are needed to control the different streams in the unit and to realize the periodic switching of the columns. Check valves (Upchurch
2.5 Results and Discussion

The objective of this section is to confirm the rules to account for extra-column dead volume, as developed above. The theoretical results obtained in the previous sections are discussed and assessed by comparison with simulation results and experimental data. Altogether a set of thirteen experimental runs was performed, eight of them in the 2-2-2-2 (runs A to H) and five in the 2-2-1-2 (runs I to M) configuration. The corresponding operating conditions in terms of $\bar{m}_j$ values and flow rates are reported in Table 2.3. In order to obtain precise values of the operating conditions it is of importance to determine the flow rates as exactly as possible. The values listed in the table were obtained by measuring the flow rates at the different ports (Feed, Desorbent, Extract, Raffinate and Outlet) throughout the entire experiment. The outlet streams were collected in small flasks over one cycle and then weighed, whilst for the inlet streams the change in weight was recorded directly with a balance. In Fig. 2.9, the operating points are shown in the $\bar{m}_2-\bar{m}_3$ plane together with the region of complete separation for the relevant linear isotherms. In all experiments, the values of $\bar{m}_1$ and $\bar{m}_4$ were fixed at specific values to fulfill the regeneration constraints. Under these conditions the SMB separation performance depends on the position of the chosen operating point in the $\bar{m}_2-\bar{m}_3$ plane only. Operating parameters used for the simulations are given in Table 2.2.
Table 2.3: Experimental conditions and results: A-H 2-2-2-2, I-M 2-2-1-2; switch time $t^\star = 3.5$ min. * Negative peak in the chromatogram of the extract did not allow for exact purity determination.

<table>
<thead>
<tr>
<th>Run</th>
<th>Effective Flow Rate Ratio [-]</th>
<th>Flow Rate [mL/min]</th>
<th>Purity [%]</th>
<th>Extract</th>
<th>Raffinate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\bar{m}_1$</td>
<td>$\bar{m}_2$</td>
<td>$\bar{m}_3$</td>
<td>$\bar{m}_4$</td>
<td>$Q_1$</td>
</tr>
<tr>
<td>A</td>
<td>3.46</td>
<td>1.59</td>
<td>2.55</td>
<td>1.13</td>
<td>1.41</td>
</tr>
<tr>
<td>B</td>
<td>3.44</td>
<td>1.64</td>
<td>2.60</td>
<td>1.10</td>
<td>1.40</td>
</tr>
<tr>
<td>C</td>
<td>3.37</td>
<td>1.71</td>
<td>2.68</td>
<td>1.03</td>
<td>1.38</td>
</tr>
<tr>
<td>D</td>
<td>3.45</td>
<td>1.91</td>
<td>2.87</td>
<td>1.12</td>
<td>1.41</td>
</tr>
<tr>
<td>E</td>
<td>3.43</td>
<td>2.15</td>
<td>3.11</td>
<td>1.09</td>
<td>1.40</td>
</tr>
<tr>
<td>F</td>
<td>3.36</td>
<td>2.21</td>
<td>3.19</td>
<td>1.05</td>
<td>1.38</td>
</tr>
<tr>
<td>G</td>
<td>3.39</td>
<td>2.35</td>
<td>3.32</td>
<td>1.08</td>
<td>1.39</td>
</tr>
<tr>
<td>H</td>
<td>3.35</td>
<td>2.40</td>
<td>3.16</td>
<td>1.04</td>
<td>1.38</td>
</tr>
<tr>
<td>I</td>
<td>3.43</td>
<td>1.90</td>
<td>3.00</td>
<td>1.12</td>
<td>1.40</td>
</tr>
<tr>
<td>J</td>
<td>3.33</td>
<td>2.19</td>
<td>3.30</td>
<td>1.03</td>
<td>1.37</td>
</tr>
<tr>
<td>K</td>
<td>3.43</td>
<td>1.89</td>
<td>2.79</td>
<td>1.04</td>
<td>1.40</td>
</tr>
<tr>
<td>L</td>
<td>3.32</td>
<td>2.38</td>
<td>3.27</td>
<td>1.01</td>
<td>1.37</td>
</tr>
<tr>
<td>M</td>
<td>3.40</td>
<td>2.45</td>
<td>3.34</td>
<td>1.08</td>
<td>1.39</td>
</tr>
</tbody>
</table>
According to the equations shown in Table 2.1 and considering the specific position of the inlet and outlet-ports (corresponding to Fig. 2.2(a), i) and 2.2(b), i)), the extra-column dead volume that one has to consider to fulfill the constraints for complete separation is, $V_D^1 = V_a + V_b + V_c$, for the 2-2-2-2 configuration, whereas for the 2-2-1-2 configuration the extra-column dead volume for section 3 has to be $V_3^D = V_F^1 + V_R^o = V_a + V_b$.

To verify experimentally the region of complete separation in the 2-2-2-2 case, the operating parameters of runs A to G were chosen on a line parallel in the diagonal of the $\bar{m}_2-\bar{m}_3$ plane. The experiments were carried out until steady state was reached; then the product streams were collected and analyzed yielding the chromatograms shown in Fig. 2.10. Figure 2.10(a) illustrates the situation at the extract port, where it can readily be seen that from run D to A, the concentration of component B in the extract increases. On the other hand, Fig. 2.10(b) shows that the A impurity in the raffinate stream increases from run D to G. This behavior is in good agreement with that predicted theoretically when considering the position of the operating points with respect to the triangle boundaries as illustrated in Fig. 2.9(a). The chromatograms can be analyzed in terms of purities for the extract and raffinate stream, which are defined by

$$P_E = 100 \times \frac{\bar{c}_{A,E}}{\bar{c}_{A,E} + \bar{c}_{B,E}},$$

$$P_R = 100 \times \frac{\bar{c}_{B,R}}{\bar{c}_{B,R} + \bar{c}_{A,R}},$$

(2.26)

where, $\bar{c}_{i,\alpha}$ is the average concentration of component $i$ in the $\alpha$ product stream ($\alpha = R, E$). The purity values listed in Table 2.3 were calculated from the chromatograms making use of a peak detection method that is part of the HPLC software. It becomes obvious from the chromatograms that an exact determination of the purities is not possible due to the shoulders of the impurities and the presence of negative peaks. Nevertheless, the trend is as expected and the lowest purities for extract and raffinate were observed at point A and G, respectively, i.e. the points that are just outside the triangle boundaries.
Figure 2.9: Region of complete separation in the \((\bar{m}_2, \bar{m}_3)\) plane: 2.9(a) operating points of runs A to H, 2-2-2-2 configuration; 2.9(b) operating points of runs I to M, 2-2-1-2 configuration.
In Fig. 2.11 the experimental data are compared with the simulation results obtained using the model of Section 2.2.2. The simulation results indicate a steep decrease of the purities at the triangle boundaries, which qualitatively is in good agreement with the experiments. A comparison between the former approach (Pedeferri et al., 1999; Abel et al., 2005) and the new one for the estimation of the extra-column dead volume is illustrated in Fig. 2.12. For the same set of experiments the $\bar{m}_3$ values are calculated twice: the previous and the present theory are represented by the filled and open symbols, respectively. For the calculation of the $\bar{m}_3$ values Eq. 2.13 is used for both approaches, however in the case of the former approach $V_j^D$ is calculated differently; $V_j^D$ is obtained by dividing the overall extra-column dead volume in section $j$ by the number of columns in this section (see Table 2.1). It can be seen that the new approach improves the agreement between simulations and experiments, particularly as far as the position of the boundary for pure raffinate is concerned. In a next step, the configuration of the unit was changed to 2-2-1-2, in order to study the effect of having one column only in section 3 (see Table 2.1). Due to the difference in the extra-column dead volume, even using the same flow rates and switch times, the effective flow rate ratio in section 3 is larger for the 2-2-1-2 configuration than for the 2-2-2-2 one. Therefore, the effective flow rate ratio $\bar{m}_3$ is shifted upwards in the operating plane, although the flow rates are the same.

If this is true, then an operating point being close to or on the boundary of pure raffinate for the 2-2-2-2 configuration moves outside the region of complete separation for the 2-2-1-2 case. By running experiments using the same flow rates for the two configurations, impure raffinate should therefore be observed for the 2-2-1-2 configuration. The purity values for both raffinate and extract stream as well as the exact operating conditions are listed in Table 2.3. The chromatograms in Fig. 2.13 show that the A impurity in the raffinate stream increases from run I to J (Fig. 2.13(a)) and from K to M (Fig. 2.13(b)). These results are consistent with the position of the operating points shown in Fig. 2.9(b). From Table 2.3, it can readily be seen that runs F and J have almost the same flow rates in section 2 and 3; however the effective
Figure 2.10: Chromatograms of the product streams at steady state conditions for runs A to G. 2.10(a) Extract A-D; Run D (—); Run C (– –); Run B (– · –); Run A (···); 2.10(b) Raffinate D-G; Run D (—); Run E (– –); Run F (– · –); Run G (···); the arrows indicate the peaks of the impurities in Extract and Raffinate.
Figure 2.11: Extract and Raffinate purities vs. $\bar{m}_3$ for runs A to G: experimental results for Extract ($\triangle$); simulation results for Extract (—); experimental results for Raffinate ($\circ$); simulation results for Raffinate (– –); boundaries of the region of complete separation (···).
flow rate ratio $\bar{m}_3$ is larger for run J (2-2-1-2). As a consequence, the raffinate purity of run J is worse compared to the one of run F. The same conclusion is obtained, when comparing run H to runs L and M. The findings are consistent with the positions of the operating points shown in Fig. 2.9. While the operating points F and H are located directly on the boundary of the region of complete separation, runs J, L, and M are outside due to the shift of $\bar{m}_3$. Additionally in order to clearly illustrate the difference between the previous and the present approach and to confirm our theoretical findings simulations were performed assuming the presence of a larger dead volume. Therefore, the volume of the tubing $c$ ($V_c$) was set to 0.6 mL which is 5 times larger than the one in our laboratory SMB unit (0.120 mL).

For the analysis of a 2-2-2-2 configuration unit with dead volume, the flow rates in section 1 and 4 were fixed and the simulations were carried out for varying flow rates in section 2 and 3. In Fig. 2.14(a), the operating conditions are shown in terms of $\bar{m}_2$ and $\bar{m}_3$. The two operating lines were calculated using

Figure 2.12: Comparison of the old and new approach for runs A to H: old approach (filled symbols); new approach (open symbols); simulation results (—).
Figure 2.13: Chromatograms of the product streams at steady state conditions for runs I to J and runs K to M. 2.13(a) Raffinate I-J; Run I (—); Run J (– –); 2.13(b) Raffinate K-M; Run K (—); Run L (– –); Run M (– · –); the arrows indicate the peaks of the impurities in the Raffinate stream.
2. Effect of extra-column dead volume in small scale SMB units

Figure 2.14: Operating conditions for the simulation with large dead volume. 2.14(a) 2-2-2-2 configuration, $Q_1 = 1.528$, $Q_4 = 0.917$ mL/min and $t^* = 3.5$ min are fixed; corresponding $\bar{m}_1$ and $\bar{m}_4$ calculated with new approach (□), old approach (■); $\bar{m}_2$-$\bar{m}_3$ line calculated with new approach (–), old approach (– –). 2.14(b) 1-2-2-2 configuration, $Q_2 = 1.147$, $Q_3 = 1.395$, $Q_4 = 0.917$ mL/min and $t^* = 3.5$ min are fixed; corresponding $\bar{m}_2$ and $\bar{m}_3$ calculated with new approach (□), old approach (■); $\bar{m}_1$ line calculated with new approach (— with ◦ end), old approach (– – with • end).
Figure 2.15: 2.15(a) Simulation results for the product purities vs. $Q_3$ (2-2-2-2 configuration): Extract (—) and Raffinate (– –) purity. 2.15(b) Simulation results for the product purities vs. $Q_1$ (1-2-2-2 configuration): Extract (—) and Raffinate (– –) purity.
the same set of flow rates; the solid and the dashed line were obtained using the present and the previous approach for the calculation of $V^D_j$, respectively. From Fig. 2.14(a), it is apparent that the dashed operating line lies outside the region of complete separation. However, as shown in Fig. 2.15(a), the simulation results for the extract and raffinate purities indicate a region of complete separation, whose boundaries are in good agreement with the position of the operating line calculated with the new approach.

In the case of a 1-2-2-2 configuration unit with dead volume, the flow rates were fixed in section 2, 3, and 4 and the simulations were carried out for varying flow rates in section 1. The operating conditions are shown in Fig. 2.14(b) and the purity values for both extract and raffinate stream are plotted in Fig. 2.15(b) as a function of the flow rate in section 1. Again, the operating lines and points shown in Fig. 2.14(b) were obtained using the same set of flow rates but a different $V^D_j$. As indicated in Table 2.1, for the new approach the value of $V^D_1$ in section 1 depends on the flow rates in section 1 and 2. From Fig. 2.15(b), it is rather clear that only when following the new approach the behavior of the plant is described correctly. For the sake of completeness it should be mentioned that a similar simulation study could be carried for a 2-2-2-1 configuration unit with the special port configuration (Outlet port before Raffinate port) and the same conclusion could be drawn.

2.6 Concluding remarks

In conclusion the modeling results and the presented experiments support the method for the calculation of extra-column dead volume derived in this Chapter. The formulas given in Table 2.1 should be used when designing SMB separations, together with Eq. 2.13 and the relevant conditions on the $\bar{m}_j$ values provided by the triangle theory. We believe this is an important detail in the theory and practice of SMB separations whenever one carries out separations using small scale laboratory SMB units. Moreover, it has been the first time that a racemic mixture of $(\pm)$-3,5-bis[1-(4-methoxyphenyl)-1-
2.6 Concluding remarks

methyl]hepta-3,4-diene-1,6-diyne could be successfully separated into its pure components for further use in the laboratory of the organic chemistry department at ETH Zurich.
2.7 Nomenclature

$c_i$ fluid phase concentration of component $i$
$d_c$ diameter of the column
$D_{ap,i}$ apparent dispersion coefficient of component $i$
$D_i$ axial dispersion coefficient of component $i$
$D^D$ dispersion coefficient in the tubing
$H_i$ Henry constant of component $i$
HETP height equivalent to a theoretical plate
$k_{s,i}a_v$ mass transfer coefficient of component $i$
$L$ length of the column
$m_j$ flow rate ratio in section $j$
$\bar{m}_j$ effective flow rate ratio in section $j$
$n_i$ adsorbed phase concentration of component $i$
$N$ number of theoretical plates
$P$ purity
$Q_j$ volumetric flow rate in section $j$
$t$ time coordinate
$t^*$ switch time
$t^r$ retention time
$\bar{t}^r$ effective retention time
$u$ superficial velocity in the column
$u^D$ superficial velocity in the tubing
$V$ volume of a column
$W$ peak width at half hight
$z$ axial coordinate
$\Delta z$ spatial grid size of the column
$\Delta z^D$ spatial grid size of the tubing

Greek Letters

$\epsilon^*$ overall bed void fraction
2.7 Nomenclature

\[ \epsilon_b \] inter particle void fraction
\[ \epsilon_p \] intra particle void fraction

**Subscripts and Superscripts**

A component A
B component B
i component index
j section index
D dead volume
2. Effect of extra-column dead volume in small scale SMB units
Chapter 3

General concept of ’cycle to cycle’ control for SMBs

3.1 Introduction

As already mentioned in Chapter 1 there is good reason for the development of an SMB controller. On the one hand SMB provides many advantages: higher productivity and lower solvent consumption compared to batch chromatography; SMB units can easily be scaled up from laboratory to pilot and production plant scale which makes the technology especially attractive for pharmaceutical industry where time to market is a crucial factor; development of a new SMB separation takes only a few month compared with a few years for the design of an enantioselective synthesis, and last but not least SMB allows to separate compounds characterized by very low selectivities which is often the
case for chiral molecules. On the other hand the robust and optimal operation of an SMB unit is still a challenge for many reasons: change in ambient conditions, e.g. temperature fluctuations that influence the thermodynamics of adsorption; aging of the stationary phase material; uncertainties in the process itself during the course of a separation campaign, e.g. pump disturbance. What makes the situation even more complex is the fact that regulatory agencies such as the Federal Food and Drug Administration and the European Medicines Agency have enforced strict regulations on the purity requirements of single enantiomer drugs. The development of a suitable controller could address the above mentioned problems and the strict regulations enforced by the regulatory agencies.

Therefore, in literature different control schemes have been proposed over the last years to optimize the operating conditions to utilize the full economic potential of the SMB process (Kloppenburg and Gilles, 1999a; Klatt et al., 2000, 2002; Schramm et al., 2003a; Wang et al., 2003; Toumi and Engell, 2004; Song et al., 2006c,a,b; Engell, 2007). However, the drawback of most of these approaches is the need for accurate adsorption data of the system. However, the determination of the complete adsorption behavior can be a lengthy and challenging task itself which is in conflict with the industry interest to enter the market as soon as possible.

A significant feature of the controller developed in our group is that it only requires minimal information about the system, namely the overall void fraction of the columns and the linear adsorption behavior of the mixture to be separated. It has been proven by extensive simulations that the controller is able to fulfill the process specifications and to optimize the separation performance for mixtures subjected to linear (Abel et al., 2004b; Erdem et al., 2004c), Langmuir (Erdem et al., 2004a) and generalized Langmuir isotherms (Grossmann et al., 2008a). The effectiveness of the controller has also been demonstrated experimentally, on achiral systems subject to linear isotherms (Abel et al., 2005; Erdem et al., 2005, 2006) and on chiral systems with Langmuir isotherms (Amanullah et al., 2007), but never reaching high feed concentra-
3.2 'Cycle to cycle' control concept

This section presents the main ideas of the 'cycle to cycle' control concept. A detailed description of the theory behind the controller has been extensively reported (Grossmann et al., 2008b). The control concept is based on model predictive control (MPC) and a schematic of the proposed MPC concept is shown in Fig. 3.1 (Lee et al., 2001). The controller is based on a simplified SMB model that requires only the information about the overall void fraction of the columns and the Henry constants of the compounds to be separated. These parameters can be easily obtained from pulse injection experiments under diluted conditions. The simplified SMB model is obtained by applying

Figure 3.1: Scheme of the 'cycle to cycle' control concept.
a number of simplification steps to an SMB model. The SMB model is based on first principles and comprises partial differential equations describing the dynamics of each chromatographic column, algebraic equations describing the connections among them as well as the proper boundary and initial conditions. The equilibrium dispersive model is used to describe the dynamics inside each chromatographic column.

\[
\frac{\partial c_{i,h}}{\partial t} + \frac{(1 - \varepsilon_h)}{\varepsilon_h} \frac{\partial q_{i,h}^*}{\partial t} + \frac{Q_h}{A_{cr}\varepsilon_h} \frac{\partial c_{i,h}}{\partial z} = D_{ap,i} \frac{\partial^2 c_{i,h}}{\partial z^2} \quad \text{for} \quad i = A, B
\]

\[
h = 1, \ldots, n_{col}
\]

In the above equation, \(D_{ap,i}\) is the apparent axial dispersion coefficient lumping the mass-transfer resistance and axial dispersion; \(\varepsilon_h\) is the total packing porosity in the \(h\)th column; \(c_{i,h}\) is the fluid phase concentration and \(q_{i,h}^*\) is the equilibrium solid phase concentration of component \(i\) in column \(h\); \(A_{cr}\) is the column cross-section area. The variable \(Q_h\) is the flow rate in column \(h\) of the SMB unit.

The adsorption behavior of both components inside the columns is assumed to follow a linear adsorption isotherm \(q_{i,h}^* = H_i c_{i,h}\), with Henry’s constants \(H_A\) and \(H_B\), where \(A\) and \(B\) are the strongly and weakly adsorbed components, respectively. Note that Eqs. 3.1 are still nonlinear due to the convective term where the flow rate (input variable) is multiplied by the derivative of the concentration (state variable). Such nonlinear SMB model is simplified through a number of steps to a linear discrete-time reduced order dynamical model which will be referred to as simplified SMB model. The details of the simplification steps have been reported elsewhere (Grossmann et al., 2008b).

The simplified SMB model has the general form

\[
\begin{align*}
    x_{k+1} &= Ax_k + Bu_k \quad x \in \mathbb{R}^{n_x}, \ u \in \mathbb{R}^{n_u} \\
    y_k &= Cx_k + Du_k \quad y \in \mathbb{R}^{n_y}
\end{align*}
\]

where \(A, B, C\) and \(D\) are the system matrices that form the state-space
model and contain the information about the dynamics of the system at the linearization point (Grossmann et al., 2008b). The vectors $x$, $u$ and $y$ are the state, input and output of the model of dimensions $n_x$, $n_u$ and $n_y$, respectively. The index $k$ is the cycle index.

A disturbance model is included in the simplified SMB model in order to account for the unavoidable mismatch between the linear dynamics and the full nonlinear SMB model describing the real experimental plant, i.e. the plant model mismatch. Besides, the disturbance model captures the combined overall effect of all possible disturbances on the plant output which is a critical issue for the control performance. The disturbances affecting SMB units can be divided into two categories. The first one are persisting periodic disturbances with period of one cycle, e.g. changes in the feed concentration during operation due to different feed batches of the mixture to be separated. This kind of disturbances will persist throughout the operation. The second category consists of random disturbances which do not repeat every cycle. The effect of unknown model errors and both type of disturbances are incorporated as a residual term in the state vector $x$ which will be estimated using a Kalman filter. The measured variables or outputs $y$ are the product (extract and raffinate) concentrations averaged over one cycle. The manipulated variables or inputs $u$ are the four internal flow rates in the four sections of the SMB unit.

The switching time, $t^*$, is fixed in this work, it is predefined and chosen based on maximum allowable pressure drop considerations. It is worth noting, however, that the switching time has an effect on the productivity, which could be exploited by the controller for SMB optimization as shown elsewhere (Toumi and Engell, 2004; Grossmann et al., 2007)

With the simplified SMB model the controller is able to predict the future evolution of the SMB plant. Based on this the controller calculates a set of manipulated variables, i.e. flow rates, which is optimal with respect to the specified objective function, and fulfills the given product and process constraints according to the simplified SMB model. A significant feature of the controller is that its simplified SMB model requires only the linear isotherm
information, i.e. $H_A$ and $H_B$, and the overall bed porosity $\epsilon^*$ of the columns.

### 3.2.1 Formulation of the optimization problem

Due to the model-based nature of the controller it is straightforward to impose the operational constraints and the process specifications in straightforward manner within the control formulation. The controller has to fulfill two main tasks: the first and most important task of the controller is to achieve the desired minimal purities in the product streams; the second task will be to optimize the unit with respect to the cost function, or performance index. The constraint on the minimal purity specifications can be formulated as:

\[
\begin{align*}
P^\text{ave}_E &\geq P^\text{min}_E - s_1 \\
P^\text{ave}_R &\geq P^\text{min}_R - s_2,
\end{align*}
\]

(3.3)

where $P^\text{ave}_E$ and $P^\text{ave}_R$ are the extract and raffinate purities, respectively, averaged over one cycle. The non-negative slack variables $s_1$ and $s_2$ are introduced to soften the constraints on the purity specifications and to avoid infeasibility problems (Grossmann et al., 2008b). In order to check whether the conditions in Eq. (3.3) are fulfilled or not, the controller receives once per cycle the results of the concentration measurements of the two product streams. Based on this information the controller will compute the actions to be undertaken for the next process cycle.

The process constraints such as the maximal pressure drop in the unit are considered by constraining the manipulated variables with upper bounds. The maximal rate of change of the manipulated variables is constrained as well to avoid sudden and large pressure fluctuations in the unit.

\[
\begin{align*}
Q_j &\leq Q^\text{max} \\
|\Delta Q_j| &\leq \Delta Q^\text{max} \\
(j = 1, \ldots, 4),
\end{align*}
\]

(3.4)
3.2 'Cycle to cycle' control concept

where $|\Delta Q_j|$ is the flow rate change in section $j$ from one cycle to the next cycle.

The second task to be pursued is the optimization of the performance of the SMB plant by maximizing the productivity and by minimizing the solvent consumption as defined by Eqs. (5.6) and (5.7), respectively.

$$PR = \frac{Q_Fc_T^F}{n_{col}V(1-\epsilon^*)} = \frac{(m_3 - m_2)c_T^F}{n_{col}t^*}$$ (3.5)

$$SC = \frac{Q_D + Q_F}{Q_Fc_T^F} = \frac{m_1 - m_4 + m_3 - m_2}{(m_3 - m_2)c_T^F}$$ (3.6)

In above equations $Q_D$, $Q_F$, $c_T^F$ and $n_{col}$ are the desorbent flow rate, the feed flow rate, the overall feed concentration and the number of columns in the SMB unit, respectively.

Therefore, the cost function of the optimization problem is required to minimize a weighted sum of productivity and solvent consumption over one cycle and the slack variables.

$$\min_{Q_1,\ldots,Q_4,s} [(\lambda_D Q_D - \lambda_F Q_F) + \lambda_s s]$$ (3.7)

The weights $\lambda_F$ and $\lambda_D$ reflect the relative importance given to maximizing the productivity or to minimizing the desorbent consumption, respectively; the vector $\lambda_s$ contains the weight for the slack variables and the vector $s$ contains the slack variables itself. Note that beside those in Eq. (3.3), other slack variables are introduced to avoid negative values of the predicted concentrations and to minimize changes in the operating conditions for the sake of a smooth operation. A discussion on how the weights in the cost function steer the controller’s behavior has been reported in (Grossmann et al., 2008a)

The linear cost function of Eq. (3.7) together with the simplified SMB model in Eq. 3.2 and the linear constraints Eqs. (3.3) and (3.4) constitute a linear programming (LP) problem solved online once every cycle, i.e. from 'cycle to cycle'. ILOG CPLEX 10.0 (ILOG, Sunnyvale CA, USA) is a commercial LP
3. General concept of ‘cycle to cycle’ control for SMBs

solver and was used online with a computation time of about 0.1 second on a PC with a 3GHz processor. A detailed description of the solution method, including a discussion of some implementation issues that are not reported here, may be found elsewhere (Grossmann et al., 2008b).
Chapter 4

Implementation of an automated on-line HPLC monitoring system

4.1 Introduction

In the first experimental application of the 'cycle to cycle' controller to chiral separations a combination of polarimeter and UV detector was used to monitor the concentrations of the two enantiomers in both product streams averaged over one process cycle (Amanullah et al., 2007). It was found that the accuracy of the polarimeter is greatly affected by experimental disturbances, such as pressure fluctuations in the measuring cell or impurities in the system, which is a problem since the performance of the controller depends directly on the accuracy and reliability of the feedback information from the plant.

As a consequence, we have modified the monitoring system to overcome the
4. Implementation of an automated on-line HPLC monitoring system

drawbacks associated to the on-line optical detectors. This Chapter presents
the design and the implementation of a new automated on-line HPLC mon-
itoring system, which determines the average concentrations of the raffinate
and extract stream over one cycle, and communicates them as feedback infor-
mation to the controller. The HPLC analysis provides the flexibility to apply
the controller to a wider range of separation tasks. Moreover, the feedback
information is very accurate and precise and less affected by possible impu-
rities in the system. However, the HPLC measurements can be carried out
less frequently, i.e. once per cycle and the analysis time can be in the order
of the cycle time, which introduces a significant time delay in the measure-
ments. As a consequence, the controller actions are based on more accurate
but less frequent and time delayed feedback information from the plant. The
new automated on-line HPLC monitoring system was tested and implemented
in two steps. In a first step, the performance of the system was assessed mea-
suring the concentrations of both components in the product streams at each
cycle and comparing them to the final off-line analysis of the product streams.
These experiments were done without using the controller. Finally, controlled
SMB experiments were carried out to test and to benchmark the performance
of the integrated system.

4.2 On-line monitoring systems for SMBs

There exist different techniques and procedures to monitor the concentrations
of an SMB unit, which can be classified as follows. First of all, one can
distinguish between low frequency (HPLC) and high frequency (UV and po-
larimeter) sampling techniques. Secondly, both types of measurements can
be taken at two conceptually different positions of the SMB unit. The mea-
surement devices can be positioned either within the loop of the SMB unit,
i.e. between two consecutive columns, or outside the loop, i.e. at the raffi-
nate and extract outlet ports. In Table 4.1 the corresponding four different
combinations are reported with an indication about relevant publications dis-
Table 4.1: Concentration measurement techniques

<table>
<thead>
<tr>
<th>Sampling</th>
<th>Within the loop</th>
<th>Outside the loop</th>
</tr>
</thead>
<tbody>
<tr>
<td>UV / Polarimeter (High freq.)</td>
<td>(Mihlbachler et al., 2004)</td>
<td>(Zenoni et al., 2000)</td>
</tr>
<tr>
<td>HPLC (Low freq.)</td>
<td>(Araujo et al., 2008)</td>
<td>this work</td>
</tr>
</tbody>
</table>

discussing the different techniques. Not all of them were developed and applied for control purposes, but rather just for monitoring reasons. The presented automated on-line HPLC monitoring system is custom-made and consists of two main parts, namely a standard HPLC unit combined with the automated sample collecting system shown in Fig. 4.1 (Joint analytical system, Moers, Germany). It consists of a collecting system for the two product streams and a standard HPLC PAL system (CTC Analytics, Zwingen, Switzerland) used for automated sample processing. During each cycle of the process the product streams are collected in two of the four glass tanks, say E1 (Extract) and R1 (Raffinate), whereas from each of the other two tanks a sample is injected to the HPLC, with a time delay to avoid overlapping of the peaks. The HPLC automatically analyzes the samples and returns the concentration values of the two species in both product streams, i.e. the feedback information for the controller. In the next cycle the role of the tanks is switched. A detailed description of the method of operation of the on-line monitoring system will be presented in Section 4.3.3.

4.3 Experimental

4.3.1 SMB unit

The laboratory SMB unit was set up according to the 2-2-2-2 configuration shown in Fig. 4.2, where the possibility of an open or closed loop system is also
4. Implementation of an automated on-line HPLC monitoring system

Figure 4.1: Process flowsheet for the automated on-line HPLC monitoring system. Position 1 and Position 2 indicate the possible valve positions for W1 to W4. Thick lines indicate fluid flow and thin lines gas flow.
indicated. The latter configuration was implemented for the control experiments, whereas for the uncontrolled runs (testing of the new HPLC monitoring system) the open loop configuration was used. The SMB unit is located in a temperature controlled room to assure isothermal operating conditions at $T = 23^\circ C$. In addition the column compartment of the HPLC is temperature controlled and kept at $23^\circ C$. From the scheme, it can be seen that the SMB unit is built up connecting equal sub-units (inlet port, column, outlet port, and connecting tubing parts) in series. The extra-column dead volume for all four sections is the same: $V_j^D (j = 1, \ldots, 4) = V^D = 0.133 \text{ ml}$ (Katsuo et al., 2009b). The dead volume is accounted for in the calculation of the key operating parameters of an SMB, i.e. the flow rate ratios $m_j$, as follows (Migliorini et al., 1999b):

$$m_j = \frac{Q_j t^* - V \epsilon^* - V_j^D}{V (1 - \epsilon^*)} \quad (j = 1, \ldots, 4). \quad (4.1)$$

Figure 4.2: Scheme of the 2-2-2-2 laboratory scale SMB plant. The dashed line indicates the possibility of an open or closed loop system.
4. Implementation of an automated on-line HPLC monitoring system

4.3.2 Materials and characterization

For the experiments a racemic mixture of Guaifenesin enantiomers (Fludan, Vankleek Hill, Canada) was used. The separation was carried out on CHIRALCEL™ OD (Chiral Technologies Europe, Illkirch, France), a cellulose based chiral stationary phase (cellulose tris (3,5-dimethylphenylcarbamate) coated on silica support), in ethanol (Amanullah et al., 2007). The material has a particle size of 20 µm and was slurry packed in 8 standard stainless steel columns (10 cm × 1 cm), with a mobile phase mixture of 95/5 % v/v ethanol and 2-propanol. The packing was carried out for 40 min with a flow rate of $Q = 46$ ml/min. Under these conditions the pressure drop along the column is 36 bar and below the maximum allowable pressure of 40 bar for this stationary phase.

The overall void fraction of the columns $\epsilon^*$ is determined by a pulse injection of a non-retained compound, in this case a solvent mixture in pure ethanol mobile phase, and measuring its retention time, and calculated as:

$$\epsilon^* = \frac{t_0 Q}{V},$$  \hspace{1cm} (4.2)

where $t_0$, $Q$, and $V$ are the retention time of the non-retained compound, the volumetric flow rate, and the column volume, respectively, and the extra-column dead volume of the HPLC has been taken into account. The Henry constants $H_i$ of the two enantiomers were calculated from the retention time of the two components obtained under diluted conditions, i.e.

$$H_i = \frac{\epsilon^*}{1 - \epsilon^*} \left( \frac{t_{R,i} - t_0}{t_0} \right), \quad (i = A, B).$$  \hspace{1cm} (4.3)

In the equation above $t_{R,i}$ is the residence time of component $i$ corrected with the dead time of the HPLC. From now on, the more and the less retained enantiomer will be referred to as component A and B, respectively.

Table 5.1 summarizes the results for the eight columns installed in the laboratory SMB unit. The averaged values reported in Table 5.1 will be used for
calculations, representations in the \((m_2, m_3)\) plane and for simulations.

Table 4.2: Column test with ethanol as mobile phase and CHIRALCEL\textsuperscript{TM} OD as stationary phase at 23\degree C; \(c_A = c_B = 0.01\ \text{g/L}; V_{\text{inj}} = 20\ \mu\text{l}; Q=1\ \text{mL/min.}\)

<table>
<thead>
<tr>
<th>Column No.</th>
<th>(H_B)</th>
<th>(H_A)</th>
<th>(\epsilon^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.51</td>
<td>1.10</td>
<td>0.75</td>
</tr>
<tr>
<td>2</td>
<td>0.49</td>
<td>1.10</td>
<td>0.75</td>
</tr>
<tr>
<td>3</td>
<td>0.50</td>
<td>1.10</td>
<td>0.74</td>
</tr>
<tr>
<td>4</td>
<td>0.48</td>
<td>1.06</td>
<td>0.75</td>
</tr>
<tr>
<td>5</td>
<td>0.52</td>
<td>1.12</td>
<td>0.75</td>
</tr>
<tr>
<td>6</td>
<td>0.51</td>
<td>1.10</td>
<td>0.75</td>
</tr>
<tr>
<td>7</td>
<td>0.48</td>
<td>1.08</td>
<td>0.74</td>
</tr>
<tr>
<td>8</td>
<td>0.51</td>
<td>1.10</td>
<td>0.74</td>
</tr>
<tr>
<td>average</td>
<td>0.50</td>
<td>1.10</td>
<td>0.75</td>
</tr>
</tbody>
</table>

4.3.3 On-line monitoring

The process flowsheet for the automated sample collecting system is shown in Figure 4.1. The main components are four air-actuated 4-port 2-position valves W1 to W4 (VICI, Schenkon, Switzerland), eight magnetic electrically-actuated on-off valves V1 to V8 (Kuhnke, Malente, Germany), one magnetic electrically-actuated 3-way 2-position valve T1 (Kuhnke, Malente, Germany), one solvent pump (Pump1), three vessels for product collection and solvent storage, and four custom-made glass tanks (E1, E2, R1, R2) to collect the product fractions over a defined period of time. Because of its good chemical resistance and ease of operation PEEK material was used for the connections. Note that in Fig. 4.1, the thick lines represent the fluid streams and the thin ones the gas streams (from the nitrogen cylinder).

The HPLC PAL system used for the sample injection is equipped with an electrically-actuated 6-port 2-position injection valve (VICI, Schenkon,
4. Implementation of an automated on-line HPLC monitoring system

Switzerland), a washing station for the syringe, and is connected to an HPLC unit (Agilent LC 1200, Santa Clara, USA). The automated sample collecting system is operated through the PAL Cycle Composer Control software (CTC Analytics, Zwingen, Switzerland).

In the following, the mode of operation of the automated on-line HPLC monitoring system (referred as AMS system) is explained for two consecutive cycles. The two cycles are divided in 10 different steps and for each step (S1 to S10) the specific configuration of the valves is listed in Table 4.3. For instance, S1 in Table 4.3 refers to the step where sample is injected from E2 and R2 and product collected in E1 and R1. The AMS system fulfills two different tasks that are always performed in parallel; namely collecting the extract and raffinate stream of the ongoing cycle and analyzing the product streams of the previous cycle. During the process cycles with odd index (W1 to W4 in “Position 1”) the product streams are collected in the glass tanks E1 (Extract) and R1 (Raffinate), whereas for analysis the ATC arm of the PAL system injects samples from tanks E2 and R2 to the HPLC (see Fig. 4.1). In the following the different steps of the analyzing procedure are explained briefly; details about the configuration of the valves are shown in Table 4.3. For explanation, the valves V1 to V8 are closed in “off” position and if valve T1 is in position “1” the solvent is circulated back to the storage tank, as shown by the dashed line in Fig. 4.1.

At first samples from E2 and R2 are injected to the HPLC; the extract sample is always injected first. In the next step the two tanks are pressurized with nitrogen so as to speed up the draining. Before being used for another collecting period E2 and R2 need to be cleaned with pure solvent, see step S3 in Table 4.3. In the last two steps (S4 and S5) the tanks are emptied and then depressurized to be ready for the next collecting period. In the meantime, the HPLC automatically analyzes the samples from E2 and R2 and returns the composition of the product streams in terms of the peak area. Making use of an experimentally determined calibration curve the areas are converted into concentrations, required as feedback information by the controller.
For the next process cycle (even index) the situation is vice versa, the products are now collected in E2 and R2 and samples are taken from E1 and R1 (W1 to W4 in ”Position 2”). The valve settings for the next steps are listed in Table 4.3 and together with Fig. 4.1 one can easily follow the different steps. The process described, for collecting and sampling over two consecutive cycles, can be repeated for the desired amount of process cycles.

The time required for HPLC analysis of the samples needs to be smaller than the cycle time of the SMB process, otherwise the HPLC would not be ready for the next sample injection at the beginning of a new cycle. Moreover, the time between the sample injection from the extract and raffinate tanks needs to be chosen long enough to assure baseline separation. Hence, the injection procedure needs to be tuned to fulfill these constraints. A good compromise between retention time and peak resolution was found at a solvent composition of 60/40 % v/v ethanol and heptane using an analytical CHIRALCEL™ OD column (25 cm × 0.46 cm). A typical chromatogram of the two successive product samples (extract and raffinate) can be seen in Fig. 4.3. Note that this monitoring system gives the flexibility to use different solvents and stationary phases for the analysis in the HPLC and for the SMB unit, as it is the case in this work. However, the injection of a sample with a different solvent composition than the one present in the HPLC might generate additional peaks in the chromatogram. This issue has to be addressed in the development of the analyzing procedure.

4.4 Results and discussion

4.4.1 Open-loop uncontrolled SMB operation

The purpose of this part of the work is to test and verify both the newly developed automated on-line HPLC monitoring system and the separation performance of the SMB unit, not yet applying the controller. The linear complete separation region in the \((m_2, m_3)\) plane shown in Fig. 4.4(a) is obtained using
Table 4.3: Control board for the valve positions of two consecutive cycles.

<table>
<thead>
<tr>
<th>Step</th>
<th>E1</th>
<th>E2</th>
<th>R1</th>
<th>R2</th>
<th>W1</th>
<th>W2</th>
<th>W3</th>
<th>W4</th>
<th>V1</th>
<th>V2</th>
<th>V3</th>
<th>V4</th>
<th>V5</th>
<th>V6</th>
<th>V7</th>
<th>V8</th>
<th>T1</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>sample inj.</td>
<td>draining</td>
<td></td>
<td>sample inj.</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>off</td>
<td>off</td>
<td>off</td>
<td>off</td>
<td>off</td>
<td>off</td>
<td>off</td>
<td>off</td>
<td>off</td>
</tr>
<tr>
<td>S2</td>
<td>fill</td>
<td>with extract product</td>
<td>draining</td>
<td>fill with raffinate product</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>off</td>
<td>off</td>
<td>off</td>
<td>off</td>
<td>off</td>
<td>on</td>
<td>off</td>
<td>off</td>
<td>off</td>
</tr>
<tr>
<td>S3</td>
<td>draining</td>
<td></td>
<td></td>
<td>fill with solvent</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>off</td>
<td>off</td>
<td>off</td>
<td>off</td>
<td>off</td>
<td>on</td>
<td>off</td>
<td>off</td>
<td>off</td>
</tr>
<tr>
<td>S4</td>
<td>wait</td>
<td></td>
<td></td>
<td>draining</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>off</td>
<td>off</td>
<td>off</td>
<td>off</td>
<td>on</td>
<td>off</td>
<td>on</td>
<td>on</td>
<td>off</td>
</tr>
<tr>
<td>S5</td>
<td></td>
<td></td>
<td></td>
<td>wait</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>off</td>
<td>off</td>
<td>off</td>
<td>off</td>
<td>off</td>
<td>on</td>
<td>off</td>
<td>on</td>
<td>off</td>
</tr>
<tr>
<td>S6</td>
<td>sample inj.</td>
<td></td>
<td></td>
<td>sample inj.</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>off</td>
<td>off</td>
<td>off</td>
<td>off</td>
<td>off</td>
<td>off</td>
<td>off</td>
<td>off</td>
<td>off</td>
</tr>
<tr>
<td>S7</td>
<td>draining</td>
<td></td>
<td></td>
<td>fill with solvent</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>on</td>
<td>off</td>
<td>on</td>
<td>off</td>
<td>off</td>
<td>on</td>
<td>off</td>
<td>off</td>
<td>on</td>
</tr>
<tr>
<td>S8</td>
<td>fill</td>
<td>with extract product</td>
<td></td>
<td>fill with raffinate product</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>off</td>
<td>off</td>
<td>off</td>
<td>off</td>
<td>off</td>
<td>on</td>
<td>off</td>
<td>off</td>
<td>on</td>
</tr>
<tr>
<td>S9</td>
<td>draining</td>
<td></td>
<td></td>
<td>draining</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>on</td>
<td>off</td>
<td>on</td>
<td>off</td>
<td>off</td>
<td>on</td>
<td>off</td>
<td>off</td>
<td>on</td>
</tr>
<tr>
<td>S10</td>
<td>wait</td>
<td></td>
<td></td>
<td>wait</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>off</td>
<td>off</td>
<td>off</td>
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<td>off</td>
<td>off</td>
<td>on</td>
<td>off</td>
<td>on</td>
</tr>
</tbody>
</table>
4.4 Results and discussion

the average Henry constants reported in Table 5.1. All experiments were carried out at a constant switch time of 2.00 min, and the operating conditions in terms of $m_j \ (j = 1, \ldots, 4)$ are listed in Table 4.4; $m_1$ and $m_4$ were chosen so as to guarantee complete regeneration of the stationary phase and the mobile phase, respectively. Moreover, the same low total feed concentration was used for all experiments, namely 0.1 g/L, to ensure linear adsorption conditions. For the calculation of the effective flow rate ratios Eq. 5.8 is used, which takes into account the effect of extra-column dead volume. The position of the experimental points in the $(m_2, m_3)$ plane is shown in Fig. 4.4(a).

The mode of operation of the newly developed automated on-line HPLC monitoring system was assessed by recording the purities of both components in the extract and raffinate stream averaged over one cycle. As shown in Table 4.4, the results at steady state operation (cycle 14) were then compared to off-line HPLC analysis carried out on the samples collected along cycle 15. In

Figure 4.3: Typical chromatogram of the two successive product samples (Extract and Raffinate) at a flow rate of 0.73 ml/min and a wavelength of 265 nm.
Table 4.4: Operating conditions and on-line/off-line purities at steady state for experimental runs 1 to 4. In all runs $c_F=0.1$ g/L and $t^*=2.00$ min.

<table>
<thead>
<tr>
<th>Run</th>
<th>$m_1$</th>
<th>$m_2$</th>
<th>$m_3$</th>
<th>$m_4$</th>
<th>$P^\text{on}_E$</th>
<th>$P^\text{on}_R$</th>
<th>$P^\text{off}_E$</th>
<th>$P^\text{off}_R$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.362</td>
<td>0.332</td>
<td>0.682</td>
<td>0.022</td>
<td>67.8%</td>
<td>100.0%</td>
<td>69.3%</td>
<td>100.0%</td>
</tr>
<tr>
<td>2</td>
<td>1.307</td>
<td>0.432</td>
<td>0.782</td>
<td>0.032</td>
<td>94.3%</td>
<td>100.0%</td>
<td>94.0%</td>
<td>100.0%</td>
</tr>
<tr>
<td>3</td>
<td>1.382</td>
<td>0.58</td>
<td>0.932</td>
<td>0.202</td>
<td>100.0%</td>
<td>100.0%</td>
<td>100.0%</td>
<td>100.0%</td>
</tr>
<tr>
<td>4</td>
<td>1.572</td>
<td>0.782</td>
<td>1.152</td>
<td>0.222</td>
<td>100.0%</td>
<td>86.3%</td>
<td>100.0%</td>
<td>87.1%</td>
</tr>
</tbody>
</table>

Figure 4.4: (a) Region of complete separation for Guaifenesin enantiomers in ethanol at 23°C and the position of the operating points 1 to 4. (b) Off-line and on-line measurements of the product purities vs. $m_2$ for the operating points 1 to 4. The dotted line indicates the ideal boundary of the complete separation region.
4.4 Results and discussion

Fig. 4.4(b) the purity values are shown as a function of $m_2$; the off-line purity measurements (filled markers connected by a solid line) are in good agreement with the ones obtained from the new on-line monitoring system (open markers connected by a dashed line), thus demonstrating its functionality.

The results in Fig. 4.4(b) indicate that with increasing $m_2$ values the extract purities increase, whereas the raffinate purities decrease. In run 3 complete separation was achieved, i.e. no impurities could be detected in the HPLC analysis. By comparing Figs. 4.4(a) and 4.4(b), it is apparent that the experimental separation performance of the SMB is in agreement with the linear region of complete separation predicted by the triangle theory (Mazzotti et al., 1997).

4.4.2 Closed-loop controlled SMB operation: linear conditions

Due to temperature deviations, changes in the packing characteristics and dead volume the operation of SMB units is subjected to uncertainties in the retention behavior of the species to be separated. Nevertheless, the controller should still be able to fulfill the product specifications under these conditions. In order to simulate this situation, i.e. to introduce a plant/model mismatch the controller was developed using Henry constants that are different from the measured ones (see Table 5.1). For the design of the controller the following Henry constants were used: $H_A = 1.25$ and $H_B = 0.61$. This is true for all the cases presented in the following.

**Case study 1: set point tracking for different initial operating conditions**

The aim of this section is to demonstrate the ability of the controller to fulfill the product specifications and to improve performance in a similar way independently of the initial conditions of the plant. To this aim runs A to D
were carried out, where the plant was started up from four different operating points, the controller was switched on at cycle 5, as illustrated in Figs. 4.5 and 4.6, the total feed concentration of Guaifenesin was 0.75 g/L, the switch time was 2.00 min and the purity specifications were 98.5% for both product streams. Figure 4.5 reports the operating trajectories in the \((m_2, m_3)\) plane, and shows that for all four runs the final operating points reached by the controller are very close, as demonstrated also by the final \(m_2\) and \(m_3\) values listed in Table 5.2; they deviate by less than 1.5% from each other. Figure 4.6 shows the time evolution of extract and raffinate purities and of the performance indexes \(P.I.\) as a function of the time, measured in cycles. The performance index \(P.I.\) reflects the process performance in terms of solvent consumption and productivity and is defined as \(P.I. = (\lambda_D Q_D - \lambda_F Q_F)\), with \(\lambda_D = 4\) and \(\lambda_F = 20\). From Figs. 4.5 and 4.6, it is apparent that the controller ...

Figure 4.5: Trajectories of the operating points for runs A to D. The zoom illustrates the position of the final operating points indicated with the filled markers.

first drives the operation towards the region of complete separation to fulfill the product purities. Once the product specifications are achieved, within less than 20 cycles for all four runs, the performance index is gradually decreased...
4.4 Results and discussion

Figure 4.6: Purities of the product streams and performance index (P.I.) as a function of time measured in cycles for the operating points shown in Fig. 4.5. Total feed concentration $c_F = 0.75$ g/L.

Table 4.5: Initial and final operating conditions for runs A to D in terms of $m_j \ (j = 1, \ldots, 4)$ and the final value of the P.I.

<table>
<thead>
<tr>
<th>Run</th>
<th>Initial values</th>
<th>Final values</th>
<th>P.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$m_1$</td>
<td>$m_2$</td>
<td>$m_3$</td>
</tr>
<tr>
<td>A</td>
<td>1.210</td>
<td>0.233</td>
<td>1.231</td>
</tr>
<tr>
<td>B</td>
<td>1.210</td>
<td>0.437</td>
<td>1.231</td>
</tr>
<tr>
<td>C</td>
<td>1.199</td>
<td>0.233</td>
<td>1.036</td>
</tr>
<tr>
<td>D</td>
<td>1.210</td>
<td>0.436</td>
<td>1.048</td>
</tr>
</tbody>
</table>
by increasing the feed flow rate and by reducing the solvent consumption. For all four runs the controller achieves almost the same performance index (see Table 5.2), however the number of cycles needed to do so varies with the location of the start up point in the \((m_2, m_3)\) plane, as shown in Fig. 4.6. Taking into account the non-ideality of the system, e.g. axial dispersion, mass transfer resistance and differences among the columns, it can be concluded that the final operating points of our experiments are close to the point of maximum productivity predicted by the triangle theory, i.e. the vertex of the triangle of complete separation (Mazzotti et al., 1997). This set of experiments proves that the final operating point reached by the controller is unique and does not depend on the initial operating conditions.

**Case study 2: disturbance rejection**

The following experiments address one of the common problems observed in SMB separation, namely the malfunctioning of pumps during operation. Two different scenarios of pump malfunctioning are discussed, i.e. a feed pump and a recycle pump disturbance. The latter is the more challenging one since the recycle pump is located before section 1 and therefore affects the flow rates in all four sections of an SMB. Both disturbances are introduced by changing the calibration of the corresponding pump during the ongoing experiment. As a consequence, the flow rates dictated by the controller differ from the ones implemented in the SMB unit. Therefore, after introducing these permanent disturbances the controller is confronted with an SMB unit governed by different dynamics than before. Note that these disturbances are unknown to the controller and the controller experiences their effect only through the feedback information from the plant. The operating conditions in terms of total concentration, switch time and purity requirement are the same as in case study 1.

**Feed pump disturbance** The steady state operation was disturbed by changing the calibration of the feed pump, i.e. from cycle 105 on the feed
4.4 Results and discussion

The pump delivers 10% more flow (see Fig. 4.7(a)) than dictated by the controller. In order to analyze the performance of the controller under such circumstances, it is important to qualitatively understand the impact of such a disturbance on the SMB separation. An increase of the feed flow rate leads to an increase of the flow rates in sections 3 and 4, which corresponds to an upward shift of the operating point in the \((m_2, m_3)\) plane, as shown in Fig. 4.7(b). The operating point is shifted towards the region of pure extract resulting in a decrease of the raffinate purity. The solid line in Fig. 4.7(b) shows the operating trajectories after the disturbance. From Fig. 4.7(a) it is rather clear that the controller manages to recover the product purity specifications. Figure 4.9(a) shows the flow rates in section 2 and 3 and the feed flow rate as a function of the process time. The disturbance rejection behavior of the controller reflects its two main tasks and can be divided in two steps. At first, the controller decreases the feed flow rate to recover the raffinate purity as fast as possible; as a consequence the performance index \(P.I.\) increases, i.e. it gets worse. Once the minimum purity requirements are fulfilled the controller begins to optimize the process by increasing the feed flow rate, and as a result the performance index gradually decreases. At the end of this process the flow rates \(Q_2\) and \(Q_3\) as well as the feed flow rate are almost the same as before the disturbance, as it can be seen in Fig. 4.9(a). However, the performance index achieved at the end of the disturbance rejection differs from the one present before the disturbance. This can be explained by the fact that due to the disturbance, the dynamics of the plant have changed and therefore, the controller has to optimize a different plant.

**Recycle pump disturbance** In this case the calibration of the recycle pump was changed at cycle 62 so as to increase the flow rate delivered by the recycle pump by 4%. The time evolution of the purities and the performance index can be seen in Fig. 4.8(a). If the recycle pump starts to deliver higher flow rates, the flow rates in all four sections of the SMB are increased and the operating point is shifted up to the right in the \((m_2, m_3)\) plane (see Fig. 4.8(b)). Again, the operating point is shifted towards the region of pure...
4. Implementation of an automated on-line HPLC monitoring system

Figure 4.7: Feed pump disturbance. (a) Purities of the product streams and performance index (P.I.) as a function of time measured in cycles. After 105 cycles the feed pump delivers 10% more than its set point. Total feed concentration $c_F = 0.75$ g/L. (b) Shift of the operating point in the $(m_2, m_3)$ plane due to the feed pump disturbance: trajectory of the operating conditions after (—) and before (– —) the disturbance; operating point before and after the disturbance (∇).
4.4 Results and discussion

extract, which makes the purity of the raffinate go down but within less than 20 cycles the controller recovers the specifications, as shown in Fig. 4.8(a).

From Fig. 4.9(b), it is apparent that the flow rate in section 2 is affected by the recycle pump disturbance. In order to recover the raffinate purity as fast as possible the controller decreases the feed flow rate and in the second step of the disturbance rejection it slowly increases the feed flow rate to improve the process performance. The difference in the value of the performance index before and after the disturbance can be explained in the same way as discussed in the paragraph on the feed pump disturbance.

**Case study 3: Disturbance rejection and change in purity requirements at higher feed concentrations** Another controlled SMB run is carried out to demonstrate that the controller is able to reject disturbances, to fulfill changing product specifications and to optimize the process performance also at higher total feed concentration, namely 4.0 g/L. The plant is started up and after 25 cycles the controller is switched on to achieve the specified purities of 98% for the raffinate and 99% for the extract. Fig. 4.10 illustrates the results for the product purities and the performance index as a function of the time measured in cycles. Within 60 cycles after the start up the controller fulfills the minimum purity requirements and begins to improve the process performance. At cycle 112 the purity specification for the raffinate is changed to 99%, whereas the one for extract is kept constant at 99%. It can be seen in Fig. 4.10 that within 15 cycles the controller fulfills the new product specifications at the cost of the performance index. After 160 cycles the steady state operation of the unit was disturbed by increasing the feed flow rate by 10%. At the expense of the performance index the controller recovers the product purities within approximately 15 cycles and returns to steady state operation. It is worth mentioning that all these tests were done in one experiment which was continued for 260 cycles, i.e. 70 hours of continuous operation.

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Figure 4.8: Recycle pump disturbance. (a) Purities of the product streams and performance index ($P.I.$) as a function of time measured in cycles. After 62 cycles the recycle pump delivers 4% more than its set point. Total feed concentration $c_F = 0.75$ g/L. (b) Shift of the operating point in the $(m_2, m_3)$ plane due to the recycle pump disturbance: trajectory of the operating conditions after (—) and before (– –) the disturbance; operating point before and after the disturbance (▽).
4.4 Results and discussion

Figure 4.9: (a) Internal flow rates for the central sections of the SMB plus the feed pump flow rate for the rejection of the feed pump disturbance. (b) Internal flow rates for the central sections of the SMB plus the feed pump flow rate for the rejection of the recycle pump disturbance. The dotted lines indicate the occurrence of the disturbances.
Figure 4.10: Purities of the product streams and performance index (P.I.) as a function of time (measured in cycles). Total feed concentration $c_F = 4 \text{ g/L}$. After 112 cycles the purity specification for the raffinate is changed to 99% and at cycle 160 the steady state operation is disturbed by increasing the feed flow rate by 10%.
4.5 Concluding remarks

In this Chapter the development of an automated on-line HPLC monitoring system, and its experimental implementation on our laboratory SMB unit has been presented for the separation of Guaifenesin enantiomers. The monitoring was designed to determine the average concentrations of both product streams over one cycle, required as feedback information for the ‘cycle to cycle’ controller. The separation has been carried out in a four section SMB unit in the 2-2-2-2 configuration using CHIRALCEL\textsuperscript{TM} OD as stationary phase and pure ethanol as mobile phase. A set of experiments was carried out to assess the performance of the controller for different operation scenarios.

The results presented in section 4.4.1 demonstrate that the newly developed automated on-line HPLC monitoring system allows to obtain very accurate and precise concentration measurements of both product streams. Moreover, it overcomes the problems and uncertainties reported for a system based on the use of polarimeters (Amanullah et al., 2007; Araujo et al., 2008). This is a substantial improvement compared to the old system, since the performance of the controller is greatly affected by the quality of the feedback information from the plant.

The results presented in case studies 1 to 3 have demonstrated that the ‘cycle to cycle’ controller in spite of uncertainties in the model parameters (plant/model mismatch) is able to fulfill the product specifications. Even though the plant is started up at different operating conditions, the controller not only achieves the minimum purity requirement but also drives the operation to almost the same operating point, as can be seen in Fig. 4.5. Moreover, the results show that disturbances, such as feed pump and recycle pump malfunctioning, can be successfully rejected by the controller. Note that these disturbances are unknown to the controller and its behavior is only affected by the feedback information from the plant, which could be improved a lot with the newly developed monitoring system. Furthermore, in case study 3 it is demonstrated that the controller is able to fulfill distinct purity specifications and to track
4. Implementation of an automated on-line HPLC monitoring system

changing purity requirements during operation. These results prove that de-
spite disturbances the ‘cycle to cycle’ controller together with the new on-line
monitoring system assures product quality and improves the performance of
the process in terms of feed throughput and solvent consumption.
4.6 Nomenclature

$c_i$ concentration of species $i$, [g/L]

$H_i$ Henry constants of species $i$, [-]

$L$ length of a column, [cm]

$m_j$ flow rate ratio in section $j$, [-]

$N_p$ number of theoretical plates, [-]

$P$ purity, [-]

$P.I.$ performance index [-]

$Q_j$ volumetric fluid flow rate in section $j$, [ml/min]

$s$ slack variable, [-]

$t^*$ switch time, [min]

$t_0$ retention time of non-retained species, [min]

$t_{R,i}$ retention time of component $i$, [min]

$V$ column volume, [ml]

$V_j^D$ dead volume in section $j$, [ml]

$V_D$ dead volume element, [ml]

Greek letters

$\epsilon^*$ void fraction, [-]

$\lambda_D, \lambda_F, \lambda_s$, weighting factor in cost function, [-]
4. Implementation of an automated on-line HPLC monitoring system

Subscripts and superscripts

$A$ more retained component
$B$ less retained component
$\text{ave}$ average
$D$ desorbent
$E$ extract
$F$ feed
$i$ component index
$j$ section index, ($j = 1, \ldots, 4$)
$max$ maximum
$min$ minimum
$R$ raffinate
Chapter 5

Experimental implementation: nonlinear chiral separation

5.1 Introduction

This Chapter presents the first experimental implementation and results of the 'cycle to cycle' optimizing controller for a high purity chiral SMB separation under nonlinear chromatographic conditions, i.e. at high feed concentrations up to 18.0 g/L. This is an important achievement since it is well known that the productivity of an SMB unit increases with the total feed concentration and therefore, this regime is the most interesting one for industry. The performance
of the controller is assessed and discussed for the separation of the enantiomers of the chiral compound Guaifenesin at high feed concentrations. Furthermore, different case studies, i.e. pump disturbance or changes in feed concentration, are carried out to evaluate and benchmark the performance of the controller under process conditions that can be encountered during an actual separation campaign.

5.2 Background

5.2.1 Optimal SMB operation at high total feed concentrations

This section aims at illustrating the effect of the feed concentration on the SMB operation. The impact of the total feed concentration on the optimal operation of an SMB process is exemplarily analyzed for the separation of a mixture characterized by a generalized Langmuir isotherm (Mazzotti, 2006b). To present and illustrate the ideas and further on the experimental results the triangle theory is used, a well established method to design SMB separations and to interpret SMB results (Storti et al., 1993; Mazzotti, 2006b).

In the frame of the triangle theory it can be demonstrated that at steady state conditions the key design parameters influencing the separation performance of an SMB are the dimensionless flow rate ratios \( m_j \), which are defined as follows (Mazzotti et al., 1997):

\[
m_j = \frac{Q_j t^* - V \epsilon^*}{V (1 - \epsilon^*)} \quad (j = 1, \ldots, 4). \tag{5.1}
\]

In the above equation \( V, t^*, Q_j \) and \( \epsilon^* \) are the column volume, the switch time, the flow rate in section \( j \) and the overall bed void fraction, respectively. The following criteria for the choice of the flow rate ratios \( m_j \), which if fulfilled
5.2 Background

lead to complete separation, can be derived (Mazzotti et al., 1997; Mazzotti, 2006b):

\[
\begin{align*}
    m_{1,\text{min}} &< m_1 \\
    m_{2,\text{min}} &< m_2 < m_{2,\text{max}} \\
    m_{3,\text{min}} &< m_3 < m_{3,\text{max}} \\
    m_4 &< m_{4,\text{max}}
\end{align*}
\] (5.2)

It should be noted that in general all the upper and lower bounds are functions of \( m_2 \) and \( m_3 \), the adsorption isotherm parameters and the feed concentration. A detailed analysis, derivation and description of the boundaries can be found in the literature (Mazzotti, 2006b,a).

The separation conditions can be graphically represented in a plane spanned by the flow rate ratios \( m_2 \) and \( m_3 \). Since \( m_3 \) is always larger than \( m_2 \), all feasible operating points will lie above the diagonal in the \((m_2, m_3)\) plane. The constraints given by inequalities (5.3) and (5.4) define a triangular shaped region, which corresponds to operating conditions that in the frame of equilibrium theory of chromatography will result in complete separation, provided the constraints for complete regeneration of the stationary and mobile phase (inequalities (5.2) and (5.5)) are satisfied. Figure 5.1 shows the \((m_2, m_3)\) plane for an arbitrary Langmuir-type isotherm, where complete separation regions are plotted for increasing feed concentrations as indicated by the arrow. The case of infinite dilution is represented by the solid triangle, whose upper and lower bounds are given by the Henry constants of the more and less retained component \( H_A \) and \( H_B \), respectively. As the feed concentration is increased the triangle becomes more and more narrow and bends downwards to the left (dashed lines in Fig. 5.1). Operating an SMB unit optimally is regarded in this work as maximizing the feed throughput and minimizing the solvent consumption while fulfilling the specified purities. The productivity is defined as the amount of component separated per unit time and per unit volume of
5. Experimental implementation: nonlinear chiral separation

Figure 5.1: Effect of increasing total feed concentration on the separation conditions on the $(m_2, m_3)$ plane. The point $w$ achieves the maximal feed flow rate under complete separation conditions.
stationary phase and can be written by applying Eq. (5.1) as follows:

\[
PR = \frac{Q_F c_F^E}{n_{col} V(1 - \epsilon^*)} = \frac{(m_3 - m_2) c_F^E}{n_{col} t^*},
\]

(5.6)

where \( Q_F \), \( c_F^E \) and \( n_{col} \) are the feed flow rate, the overall feed concentration and the number of columns in the SMB unit, respectively.

The solvent consumption is defined as the amount of solvent required per amount of mixture separated:

\[
SC = \frac{Q_D + Q_F}{Q_F^E} = \frac{m_1 - m_4 + m_3 - m_2}{(m_3 - m_2) c_F^E},
\]

(5.7)

where \( Q_D \) is the solvent flow rate. It can easily be seen that for a constant switch time \( t^* \) and a given mixture with constant overall feed concentration \( c_F^E \), the productivity \( PR \) and the solvent consumption \( SC \) improve by increasing the term \( (m_3 - m_2) \). Therefore, the point in the \( (m_2, m_3) \) plane that maximizes productivity and achieves complete separation for a given \( c_F^E \) is the vertex of the triangle, where \( m_2 \) and \( m_3 \) are as small and as large as possible, respectively. This point is denoted as \( w \) for one of the triangles in Fig. 5.1 and moves down to the left in the \( (m_2, m_3) \) plane as the total feed concentration is increased.

### 5.2.2 'Cycle to cycle' optimizing control

At this point it should only be mentioned that an important element of the controller is the explicit and simplified SMB model that requires only the linear isotherm coefficients, i.e. the Henry constants, and the average overall void fraction of the columns installed in the SMB unit. For more details about the "cycle to cycle" controller and the formulation of the control problem it is referred to Chapter 3 and the cited publications.
5.3 Experimental

5.3.1 Materials

A racemic mixture of Guaifenesin (Fludan, Vankleek Hill, Canada) enantiomers was separated using CHIRALCEL™ OD (Chiral Technologies Europe, Illkirch, France) as stationary phase and pure ethanol as mobile phase. This cellulose based chiral stationary phase (cellulose tris (3,5-dimethylphenylcarbamate) coated on silica) is designed for high performance separations and has a particle size of 20 µm. The material was slurry packed into stainless steel columns using a mobile phase mixture of 95/5 % v/v ethanol and 2-propanol with a flow rate of \( Q = 46 \) ml/min and 40 min packing time. The pressure drop across the column during packing was 36 bar, which is within the maximum allowable pressure of 40 bar for this stationary phase.

5.3.2 Laboratory SMB unit

The laboratory SMB unit comprises 8 semi-preparative columns (10 cm length, 1 cm diameter) with two columns in every section (2-2-2-2 configuration) and is located in a room with climate control for isothermal operation at \( T = 23^\circ C \). The unit is operated in a closed loop mode and the position of the HPLC monitoring system at the outlet ports is indicated in the Fig. 5.2. In order to account for the effect of the extra-column dead volume, the flow rate ratios \( m_j \) are calculated as follows (Migliorini et al., 1999b):

\[
m_j = \frac{Q_j t^* - V \epsilon^* - V_j^D}{V(1 - \epsilon^*)}, \quad (j = 1, \ldots, 4),
\]

where \( V_j^D \) is the extra-column dead volume in section \( j \). For all four sections of our SMB unit \( V_j^D = 0.133 \) ml. A detailed analysis and description of how to account for the dead volume can be found in an earlier publication (Katsuo et al., 2009b).
Figure 5.2: Scheme of the 2-2-2-2 laboratory scale SMB plant together with the position of the HPLC monitoring device at the two outlet ports extract and raffinate.
5.3.3 Characterization

In accordance with the purpose of this section, namely to demonstrate that with the proposed controller the knowledge of the complete adsorption isotherm is not required to operate an SMB unit fulfilling the process and product constraints, only the linear adsorption behavior of the Guaifenesin enantiomers was determined at $T = 23^\circ\mathrm{C}$. First, the overall void fraction $\epsilon^*$ was determined by measuring the retention time of a non-retained compound, in this case a solvent mixture in pure ethanol. Note that $t_0$ is obtained subtracting the dead time of the HPLC system from the retention time of the non-retained compound:

$$\epsilon^* = \frac{t_0 Q}{V}, \quad (5.9)$$

where $Q$, and $V$ are the volumetric flow rate and the column volume, respectively. The Henry constants $H_i$ of the two enantiomers were calculated from the retention time of the two components obtained under diluted conditions

$$H_i = \frac{\epsilon^*}{1 - \epsilon^*} \left( \frac{t_{R,i} - t_0}{t_0} \right) \quad (i = A, B). \quad (5.10)$$

Here, $t_{R,i}$ is the residence time of component $i$ corrected with the dead time of the HPLC system. Table 5.1 reports the results for the 8 columns together with the averaged values. The latter will be used for the calculations and the graphical representations in the $(m_2,m_3)$ plane.

A detailed description of the on-line monitoring system and the parameters for the injection procedure, e.g. flow rate in the HPLC, time between the two sample injections, can be found in Section 4.3.3 of Chapter 4.
Table 5.1: Results of the column pulse injections with ethanol mobile phase and CHIRALCEL\textsuperscript{TM} OD as stationary phase at 23° C; $c_A = c_B = 0.01$ g/L; $V_{inj} = 20 \mu l$; $Q=1$ mL/min.

<table>
<thead>
<tr>
<th>Column No.</th>
<th>$H_B$</th>
<th>$H_A$</th>
<th>$c^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.51</td>
<td>1.10</td>
<td>0.75</td>
</tr>
<tr>
<td>2</td>
<td>0.49</td>
<td>1.10</td>
<td>0.75</td>
</tr>
<tr>
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<td>0.74</td>
</tr>
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</tr>
<tr>
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<td>0.75</td>
</tr>
<tr>
<td>6</td>
<td>0.51</td>
<td>1.10</td>
<td>0.75</td>
</tr>
<tr>
<td>7</td>
<td>0.48</td>
<td>1.08</td>
<td>0.74</td>
</tr>
<tr>
<td>8</td>
<td>0.51</td>
<td>1.10</td>
<td>0.74</td>
</tr>
</tbody>
</table>

\begin{tabular}{l|l|l|l}
\hline
average & 0.50 & 1.10 & 0.75 \\
\hline
\end{tabular}

5.4 Results and discussion

The main result of this Chapter, case study 1, investigates the effect of the feed concentration on the final operating point. Therefore, a series of six experiments with increasing total feed concentration ranging from 0.75 to 18 g/L was carried out. The second and third case study aim at demonstrating the independence of the final operating point of the initial conditions as well as to assess the controller performance for disturbance rejection at high feed concentrations. The last case study presents a separation with very high purity requirements, i.e. above 99%.

The simplified SMB model of the controller is based on the information about the linear adsorption isotherm of the system to be separated, i.e. only the Henry constants and the average overall void fraction of the columns. However, at high total feed concentrations the adsorption behavior becomes non-linear. Besides, temperature deviations, extra-column dead volume, and aging of the stationary phase affect the retention behavior of the compounds to be separated. In order to mimic these realistic process uncertainties a plant/model mismatch was introduced, i.e. the controller was developed using
different Henry constants than those measured earlier, i.e. $H_A = 1.10$ and $H_B = 0.50$. Thus, in all the cases presented below the controller was designed using $H_A = 1.25$ and $H_B = 0.61$. The difference corresponds to an error of 13% and 22%, respectively, and is well above the typical measurement error. Note that the complete adsorption behavior of the system to be separated has neither been measured, nor it is known from the literature.

5.4.1 Case study 1: Controlled SMB operation at high total feed concentrations

The aim of this section is to demonstrate that the controller can deliver the specified purities and improve the process performance with the knowledge of the linear adsorption behavior only, even if the separation under investigation is governed by an unknown nonlinear adsorption isotherm.

Six different experiments were carried out with total feed concentrations of 0.75, 4.0, 8.0, 10.0, 14.0, and 18.0 g/L. For all the runs the same minimal purity requirements were specified for both product streams, namely 98.5%. This allows to track the final operating point of each control run and makes the comparison among them easier. The unit was always started up with initially clean columns, i.e. before each experiment the unit was carefully flushed with pure solvent to completely remove any adsorbed compound. All experiments were carried out at a constant switch time of $t^* = 2.00$ min, and the initial and final operating conditions in terms of $m_j$ ($j = 1, \ldots, 4$) are listed in Table 5.2. The same configuration of the controller was used in all six experiments with the controller switched on at cycle 5.

Fig. 5.3 a-f show the time evolution of extract and raffinate purities, and of the performance index ($P.I.$) as a function of the cycle number together with the trajectories of the operating conditions in the $(m_2, m_3)$ plane for the six runs A to F. The performance index to be minimized by the controller, as defined in Eq. (3.7), is the same for all the cases, with $\lambda_F = 20$, $\lambda_D = 4$ and
5.4 Results and discussion

Table 5.2: Total feed concentrations of runs A to F together with the initial and final operating conditions for runs A to F in terms of $m_j$ ($j = 1, \ldots, 4$) and the final value of the productivity $PR$. The initial values of run C' correspond to the final values of run D. Run C'' reports the values of the SMB unit right after the disturbance and once it has been rejected in case study 3.

<table>
<thead>
<tr>
<th>Run</th>
<th>$c_T^F$ [g/L]</th>
<th>Initial values</th>
<th>Final values</th>
<th>$PR$ [g/(min L)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.75</td>
<td>1.199 0.233 1.048 0.272</td>
<td>1.272 0.458 0.954 0.174</td>
<td>0.023</td>
</tr>
<tr>
<td>B</td>
<td>4.0</td>
<td>1.212 0.334 1.097 0.303</td>
<td>1.229 0.447 0.916 0.192</td>
<td>0.117</td>
</tr>
<tr>
<td>C</td>
<td>8.0</td>
<td>1.212 0.334 1.04 0.303</td>
<td>1.235 0.422 0.884 0.189</td>
<td>0.231</td>
</tr>
<tr>
<td>C'</td>
<td>8.0</td>
<td>1.243 0.414 0.876 0.182</td>
<td>1.243 0.421 0.883 0.182</td>
<td>0.231</td>
</tr>
<tr>
<td>C''</td>
<td>8.0</td>
<td>1.408 0.596 1.059 0.361</td>
<td>1.413 0.437 0.889 0.165</td>
<td>0.226</td>
</tr>
<tr>
<td>D</td>
<td>10.0</td>
<td>1.211 0.334 0.996 0.303</td>
<td>1.243 0.414 0.876 0.182</td>
<td>0.289</td>
</tr>
<tr>
<td>E</td>
<td>14.0</td>
<td>1.211 0.334 0.975 0.232</td>
<td>1.180 0.401 0.844 0.105</td>
<td>0.388</td>
</tr>
<tr>
<td>F</td>
<td>18.0</td>
<td>1.211 0.334 0.955 0.303</td>
<td>1.312 0.396 0.833 0.123</td>
<td>0.492</td>
</tr>
</tbody>
</table>
5. Experimental implementation: nonlinear chiral separation

$\lambda_s = (1000, 1000)$. The performance index plotted in all the figures contains only the economic terms and not the slack variables.
5.4 Results and discussion

![Graph showing purity and performance index vs. cycle](image)

(a) Extract and Raffinate purity,  
(b) Extract and Raffinate purity in another set of conditions.
5. Experimental implementation: nonlinear chiral separation

(c) Purity [%] vs. Cycle

(d) Purity [%] vs. Cycle

Performance index [-]
Figure 5.3: Purities of the product streams and performance index (P.I.) as a function of time measured in cycles together with the trajectories in the ($m_2, m_3$) plane for runs A to F.
From Fig. 5.3 a-f, it is apparent that for all experiments the minimum purity specification is fulfilled within less than 40 cycles and even faster in the cases of runs A, B, C and D.

The final operating points reached by the controller and that fulfill the purity specifications of 98.5%, are shown in the \((m_2, m_3)\) plane of Fig. 5.3 a-f and are denoted with a different marker for each of the runs. Plotting all the final operating points of runs A to F together in the \((m_2, m_3)\) plane as in Fig. 5.4 allows to identify a trend among them: with increasing feed concentration the final operating point that fulfills a given purity shifts towards the lower left corner of the \((m_2, m_3)\) plane, i.e. towards the origin. This is the same trend predicted by the triangle theory for the point of maximal productivity and complete separation ”\(w\)”, for systems with Langmuir-type adsorption behavior, as discussed in Section 5.2.1 and illustrated in Fig. 5.1. The productivity values reported in Table 5.2 were calculated using Eq. (5.6), together with the final values of \(m_2\) and \(m_3\). From Table 5.2, it is apparent that the productivity \(PR\) at steady state conditions increases with the total feed concentration from run A to F. This result is expected for a system following a Langmuir-type adsorption behavior (Mazzotti et al., 1997).

Two important conclusions can be drawn from this set of experiments. First, these results clearly demonstrate the capability of the controller to fulfill the process and product specifications whatever the feed concentration is and regardless of the adsorption behavior that governs the SMB process. Secondly, the impact of increasing the feed concentration on the final operating point has been demonstrated experimentally and is at least qualitatively consistent with that predicted by the triangle theory for systems governed by a Langmuir-type adsorption isotherm. The results presented here represent a major improvement compared to previously presented experimental results where the operation at high feed concentrations was made very difficult due to limitations of the monitoring device Amanullah et al. (2007).
5.4 Results and discussion

Figure 5.4: Final operating points in the \((m_2, m_3)\) plane for the Runs A to F. The points \(C\) and \(C'\) correspond to the results of case study 1 and 2, respectively. \(C''\) indicates the final operating point after rejecting a pump disturbance (case study 3).
5.4.2 Case study 2: Change of feed concentration during operation

Let us now check, whether the final operating point reached by the controller in the \((m_2, m_3)\) plane is unique for the same feed concentration when two different initial points are considered. To address this question one of the runs presented in the previous case study, namely run D, was subjected to a disturbance after reaching its final operating point.

More specifically, the total feed concentration was modified to that of run C, i.e. it was decreased at cycle 105 from 10 g/L (run D) to 8 g/L (run C). Fig. 5.5 (a) shows the time evolution of the extract and raffinate purities and the performance index \(P.I.\) as a function of the cycle number. Fig. 5.5 (b) reports the corresponding operating trajectory for experimental run D. As a result of the change in feed concentration, the extract purity drops below the specifications but is recovered within less than 20 cycles, whereas the raffinate purity increases (see Fig. 5.5 (a)). The difference between the raffinate purity and the minimum specified purity reflects the gap that can be exploited by the controller for optimization.

In the first part of experimental run D, the controller drives the operation from the initial point to the final operating point indicated with D, as can be seen in Fig. 5.5 (b). Once the feed concentration has been changed to 8 g/L, the controller successfully rejects the disturbance and moves the operating point to the position denoted with C'. For comparison the end point of experimental run C, i.e. for the experiment where the SMB unit was started up with clean columns and a feed concentration of \(c_F \equiv 8\) g/L from the beginning, is plotted as well and denoted as C. The two final operating points C and C' overlap, as demonstrated also by the final \(m_2\) and \(m_3\) values listed in Table 5.2. This result demonstrates that the final operating point in the \((m_2, m_3)\) plane fulfilling the specified purity is unique and can be reached by the controller within the experimental accuracy independently of the initial conditions.
5.4 Results and discussion

Figure 5.5: Change of feed concentration during operation. (a) Purities of the product streams and performance index (P.I.) as a function of time measured in cycles. After 105 cycles the feed concentration is reduced from 10 g/L to 8 g/L. (b) Trajectory of the operating points for experimental run D. Final operating points C and C' for the experiments in case study 1 and 2, respectively.
5.4.3 Case study 3: Disturbance rejection

This experiment addresses one of the common disturbances occurring in an SMB plant, the malfunctioning of a pump. A rather challenging scenario of this type is selected for the current case study, namely the malfunctioning of the recycle pump, which is located before section 1 and therefore has an effect on the flow rates of all four sections of the SMB. The disturbance is simulated by changing on purpose the calibration of the recycle pump during the ongoing experiment. As a result the flow rates dictated by the controller for the next process cycle differ from those actually present in the unit. Hence, the controller is confronted with an SMB unit governed by different dynamics than before. Note that this change is unknown to the controller, and that the controller only notices the disturbance by its effect on the concentration measurements.

The steady state operation of run C \((c_T^F = 8 \text{ g/L})\) was disturbed at cycle 80 by changing the calibration of the recycle pump, i.e. the recycle pump delivered 4% more flow than dictated by the controller. As a result, the flow rates in all four sections of the SMB were increased and the operating point in the \((m_2, m_3)\) plane was shifted up to the right towards the region of pure extract, as shown in Fig. 5.6(b). The corresponding m-values right after the disturbance and once the disturbance has been rejected are reported in Table 5.2 as run \(C'\). Fig. 5.6(a) illustrates the time evolution of the extract and raffinate purities and the performance index \(P.I.\) as a function of the cycle number. Figure 5.6(c) shows the sectional flow rates of the SMB unit as a function of the process time. In Fig. 5.6(a) it is observed that after the disturbance the raffinate purity drops to 83% and the extract purity increases to 100%, however within less than 20 cycles the controller recovers the purity specifications.

The two main tasks of the controller are reflected in its disturbance rejection behavior. In order to recover the raffinate purity as fast as possible the controller reduces the flow rate in section 3 (see Fig. 5.6(c)); as a consequence the performance index \(P.I.\) increases, i.e. it gets worse. As soon as the purity specification is fulfilled the controller increases the flow rate in section 3 again,
5.4 Results and discussion

Figure 5.6: Recycle pump disturbance. (a) Purities of the product streams and performance index ($P.I.$) as a function of time measured in cycles. After 80 cycles the recycle pump delivers 4% more than its set point. Total feed concentration $c_{F}^{T} = 8.0$ g/L. (b) Trajectory of the operating conditions: before disturbance (dashed line); after disturbance (solid line). (c) Internal flow rates of the SMB in mL/min for the rejection of the recycle pump disturbance.
and as a result the \( P.I. \) gradually decreases, i.e. it improves. At the end of this process the flow rates \( Q_2, Q_3 \) and \( Q_4 \) as well as the feed flow rate are essentially the same as before the disturbance, as it can be seen in Fig. 5.6(c) or by comparing the final m-values reported in Table 5.2 for runs \( C \) and \( C'' \). On the contrary, the flow rate \( Q_1 \) reaches a value that deviates 4\% from the previous one, see Fig. 5.6(c) again. This observation is consistent with the outcome of four control experiments reported previously (Langel et al., 2009), where an SMB separation problem with different initial operating flow rates reached different final values of \( Q_1 \) and \( Q_4 \) but the final values of \( Q_2 \) and \( Q_3 \) were the same in all four cases. This is also consistent with the simulation based study comparing online optimizing control and off-line optimization, where again the same values of \( Q_2 \) and \( Q_3 \) were attained by both optimization schemes, but differences up to 15\% in the final \( Q_1 \) and \( Q_4 \) values were observed (Grossmann et al., 2008a). We attribute the reason of this behavior to the following facts.

The benefit to reduce desorbent consumption by changing \( Q_1 \) has to compete with the penalty associated to the change of the same flow rate which is incorporated in the cost function of Eq. (3.7). When the current controller fulfills the purity specifications, the penalty on the control changes prevails over the former benefit and the P.I. after the disturbance turns out to be different than the one before.

5.4.4 Case study 4: Purity requirements above 99%

The on-line monitoring system used in this work is based on HPLC measurements. This analytical technique allows for precise and accurate determination of the impurities. The following case study presents a scenario that exploits this advantage of the automated on-line HPLC monitoring system and specifies rather high minimal purities for the two product streams, namely 99.25\%.

A feed mixture of \( c_F^T = 4 \text{ g/L} \) was fed to the SMB unit with initially clean columns. The evolution of the purities and of the performance index is shown in Fig. 5.7. The controller was turned on at cycle 10 and within 30 cycles the purities are brought to the specified level and are held constant for the rest of
5.5 Concluding remarks

From Fig. 5.7 it is apparent that the controller manages to fulfill the purity specifications and the final value of the performance index is $P.I. = -4.65$. This value is higher than the final value of the performance index of experimental run B with a purity specification of 98.5% (see Fig. 5.3), i.e. $P.I. = -5.13$. This was to be expected since the feed flow rate has to be reduced to achieve higher purities, which in turn results in a worse value of the performance index.

![Figure 5.7: Purities of the product streams and performance index (P.I.) as a function of time measured in cycles. Total feed concentration 4.0 g/L and purity specification 99.25%.](image)

5.5 Concluding remarks

In this Chapter, the experimental implementation of a ‘cycle to cycle’ optimizing controller in an SMB unit for chiral separations under nonlinear chromatographic conditions has been presented. The experiments were carried out in a
8-column laboratory scale SMB unit for the separation of a racemic mixture of Guaifenesin enantiomers on CHIRALCEL™ OD stationary phase using ethanol as mobile phase.

A new automated on-line HPLC monitoring system was effectively used to measure the average concentration of the product streams, which are required as feedback information by the controller. This monitoring system overcomes the limitations imposed by optical detectors used in previous works to monitor the concentrations of chiral species. Its accuracy and reliability are evident from the quality of the purity measurements presented along this Chapter and from the 900 cycles of experiments reported in the case studies, which corresponds to 10 days of non-stop operation.

The experimental runs were designed to challenge the performance of the controller under nonlinear chromatographic conditions. The experimental results have clearly validated the most valuable asset of the 'cycle to cycle' controller developed in the last years: the controller can deliver the specified purities and improve the productivity with the knowledge of the linear adsorption behavior only even if the separation at stake is governed by an unknown nonlinear adsorption isotherm and despite major disturbances in the SMB unit. This is an important achievement since the time consuming task of determining the complete adsorption isotherm of a new mixture to be separated becomes redundant. The controller and the approach presented in this work offer a fast and reliable way to set up chiral SMB separations in a shorter time.
5.6 Nomenclature

\( c_i \)  
concentration of species \( i \) [g/L]

\( H_i \)  
Henry constants of species \( i \) [-]

\( m_j \)  
flow rate ratio in section \( j \) [-]

\( n_{col} \)  
number of columns [-]

\( P \)  
purity [-]

\( PR \)  
productivity [g/(min L)]

\( Q_j \)  
volumetric fluid flow rate in section \( j \) [ml/min]

\( SC \)  
solvent consumption [L/g]

\( t^* \)  
switch time [min]

\( t_0 \)  
retention time of non-retained species [min]

\( t_{R,i} \)  
retention time of component \( i \) [min]

\( V \)  
column volume [ml]

\( V_j^D \)  
dead volume in section \( j \) [ml]

Greek letters

\( \epsilon^* \)  
overall void fraction [-]

\( \lambda_D, \lambda_F \),  
weighting factor in cost function [-]
Subscripts and superscripts

\begin{itemize}
  \item $A$ more retained component
  \item $B$ less retained component
  \item ave average
  \item $D$ desorbent
  \item $E$ extract
  \item $F$ feed
  \item $i$ component index
  \item $j$ section index, ($j = 1, \ldots, 4$)
  \item max maximum
  \item min minimum
  \item $R$ raffinate
\end{itemize}
Chapter 6

Experimental implementation: Tröger’s Base separation

6.1 Introduction

In a next step after having proven that the controller is able to perform under nonlinear operating conditions it should be demonstrated how much effort and time it requires to set up the ‘cycle to cycle’ optimizing controller and the newly developed automated on-line HPLC monitoring system for a new separation problem. We will consider the separation of a racemic mixture of Tröger’s Base, which is shown in Fig. 6.1. This Chapter describes the different steps required to set up the ‘cycle to cycle’ controller for a new separation problem, i.e. characterizing of the system, setting up the on-line monitoring system and developing the controller for the new separation of Tröger’s Base.
6. Experimental implementation: Tröger’s Base separation

In addition, the results of detailed simulations are compared to experiments in order to understand how well the simulations can predict both the steady state and the dynamic behavior of the controller under nonlinear chromatographic conditions. Furthermore, the disturbance rejection behavior of the controller is presented and discussed.

Figure 6.1: Tröger’s Base(±)2,8-dimethyl-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine.

6.2 Materials and Characterization

6.2.1 Chiral stationary phase and retention behavior

For the experiments a racemic mixture of Tröger’s Base enantiomers (provided by Bayer Technology Services GmbH, Leverkusen, Germany) was separated using CHIRALPAK™ AD (Chiral Technologies Europe, Illkirch, France), an amylose based chiral stationary phase (amylose tris(3,5-dimethylphenylcarbamate) coated on silica) and ethanol as mobile phase. The material has a particle size of 20 µm and was slurry packed in nine standard stainless steel columns (10 cm × 1 cm) by Bayer Technology Services GmbH, Leverkusen, Germany. Before installing the columns in the SMB unit, they had been checked using the HPLC to determine the Henry’s constants as well as the average void fraction of the columns to verify their uniform properties. Moreover, these parameters are required as input information.
6.2 Materials and Characterization

for the simplified model of the controller. The SMB unit is the same one as presented in Section 4.3.1 of Chapter 4.

To determine the overall void fraction of the columns pulse injection experiments are carried out injecting a non-retained compound, in this case a mixture of isopropanol and ethanol in pure ethanol, and measuring its retention time $t_0$. The overall void fraction is given by:

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

where the extra-column dead volume of the HPLC was taken into account. The Henry’s constants $H_i$ were obtained from the retention time of the two enantiomers under linear operating conditions and calculated as

$$
H_i = \frac{\epsilon^*}{1 - \epsilon^*} \left( \frac{t_{R,i} - t_0}{t_0} \right) \quad (i = A, B),
$$

where $t_{R,i}$ is the residence time of component $i$ corrected with the dead time of the HPLC. From now on the more and the less retained enantiomers will be referred to as component A and B, respectively. Table 6.1 summarizes the results; the average values were used for the controller. For the Tröger’s Base enantiomers on CHIRALPAK™ AD, using ethanol as mobile phase, the Bi-Langmuir adsorption isotherm was determined previously (Katsuo et al., 2009a):

$$
n_i = \frac{H_{i,1c_i}}{1 + \sum K_{i,1c_i}} + \frac{H_{i,2c_i}}{1 + \sum K_{i,2c_i}} \quad (i = A, B)
$$

where the values of the parameters are reported in Table 6.2, columns 2 and 3.

Although the nonlinear adsorption isotherm is not needed by the controller, hence it is not used for the experiments, it is necessary to run virtual experiments where the real plant is replaced by the detailed process model, including the complete nonlinear adsorption isotherm. However, the isotherm above was measured on different columns and on a different batch of the same stationary phase material. As a consequence, the Henry’s constants obtained through
6. Experimental implementation: Tröger’s Base separation

Table 6.1: Results of the column pulse injections with ethanol mobile phase and CHIRALPAK™ AD as stationary phase at 23°C; \( c_A = c_B = 0.01 \) g/L; \( V_{inj} = 20 \) µL; \( Q=1 \) mL/min.

<table>
<thead>
<tr>
<th>Column No.</th>
<th>( H_A )</th>
<th>( H_B )</th>
<th>( \epsilon^* )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.191</td>
<td>2.003</td>
<td>0.751</td>
</tr>
<tr>
<td>2</td>
<td>5.319</td>
<td>2.080</td>
<td>0.752</td>
</tr>
<tr>
<td>3</td>
<td>5.245</td>
<td>2.037</td>
<td>0.758</td>
</tr>
<tr>
<td>4</td>
<td>5.428</td>
<td>2.137</td>
<td>0.746</td>
</tr>
<tr>
<td>5</td>
<td>5.526</td>
<td>2.153</td>
<td>0.762</td>
</tr>
<tr>
<td>6</td>
<td>5.414</td>
<td>2.098</td>
<td>0.747</td>
</tr>
<tr>
<td>7</td>
<td>5.369</td>
<td>2.074</td>
<td>0.751</td>
</tr>
<tr>
<td>8</td>
<td>5.206</td>
<td>2.024</td>
<td>0.760</td>
</tr>
<tr>
<td>9</td>
<td>5.327</td>
<td>2.068</td>
<td>0.752</td>
</tr>
<tr>
<td>Average</td>
<td>5.336</td>
<td>2.075</td>
<td>0.753</td>
</tr>
</tbody>
</table>

Eq. 6.3 with the parameters measured earlier, i.e. \( H_i = H_{i,1} + H_{i,2} \) (\( i=A, B \)), differ from those measured for the set of columns used in this work. Though small, i.e. less than 10%, such a difference is too large to be acceptable when comparing the experimental results with the calculated ones. Therefore, for the sake of comparison between experiments and simulations under nonlinear conditions, the parameters in the numerators of Eq. 6.3 are changed in such a way that the Henry’s constants are the same as those reported in Table 6.1. Moreover, it is assumed that the relative weight of the Langmuir parts of the Bi-Langmuir isotherm is the same as in the previous measurements, and that the isotherm’s denominators remain the same. Formally, the eight new parameters (that are reported in Table 6.2, columns 4 and 5) are obtained by solving the following equations (\( i = A,B; j = 1,2 \)):

\[
H_{i,1} + H_{i,2} = (H_i)_{\text{new}} \tag{6.4}
\]

\[
\frac{H_{i,1}}{H_{i,2}} = \left( \frac{H_{i,1}}{H_{i,2}} \right)_{\text{old}} \tag{6.5}
\]
### 6.3 Uncontrolled SMB experiments

Table 6.2: Column and system parameters.

<table>
<thead>
<tr>
<th>System Characteristics</th>
<th>previous work</th>
<th>this work</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>$H_{i,1}$ [-]</td>
<td>3.99</td>
<td>1.56</td>
</tr>
<tr>
<td>$K_{i,1}$ [L/g]</td>
<td>0.0107</td>
<td>0.0132</td>
</tr>
<tr>
<td>$H_{i,2}$ [-]</td>
<td>0.986</td>
<td>0.304</td>
</tr>
<tr>
<td>$K_{i,2}$ [L/g]</td>
<td>0.601</td>
<td>0.136</td>
</tr>
<tr>
<td>$k_s,i,av$ [1/sec] a</td>
<td>1.81</td>
<td>2.96</td>
</tr>
<tr>
<td>$\epsilon_bD_{ax,i}/u$ [m] b</td>
<td>$3.01 \times 10^{-4}$</td>
<td>$3.01 \times 10^{-4}$</td>
</tr>
<tr>
<td>$\epsilon^*$ [-]</td>
<td>0.753</td>
<td>0.753</td>
</tr>
</tbody>
</table>

---

a Product of mass transfer coefficient and specific surface.

b Coefficient to determine the dispersion coefficient, where $\epsilon_b$ is the bed void fraction and $u$ the superficial velocity.

\[
K_{i,j} = (K_{i,j})_{old}, \tag{6.6}
\]

where "new" refers to the average values reported in Table 6.1 and "old" to the values in columns 2 and 3 of Table 6.2.

### 6.3 Uncontrolled SMB experiments

The purpose of the uncontrolled runs at low feed concentration is to test and verify the separation performance of the SMB unit without applying the controller and to confirm the Henry's constants reported in Table 6.1. The region of complete separation according to the triangle theory and calculated using the Henry's constants in Table 6.1 is shown in Fig. 6.2(a). All experiments were carried out at a constant switch time of 180 seconds and at a constant feed concentration of 0.75 g/L, i.e. under linear chromatographic conditions. The operating conditions in terms of $m_j$ values are listed in Table 6.3 and the corresponding operating points are also shown in Fig. 6.2(a). As far as
Table 6.3: Operating conditions and product purities for the uncontrolled experiments; in all experiments $t^* = 180$ s.

<table>
<thead>
<tr>
<th>Run</th>
<th>$m_1$</th>
<th>$m_2$</th>
<th>$m_3$</th>
<th>$m_4$</th>
<th>$P_E$</th>
<th>$P_R$</th>
</tr>
</thead>
<tbody>
<tr>
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<td>5.90</td>
<td>1.45</td>
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<td>80.2</td>
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</table>

sections 1 and 4 are concerned, $m_1$ and $m_4$ were chosen to guarantee complete regeneration of the stationary and mobile phase, respectively.

The purities of the extract and raffinate averaged over one cycle at steady state are reported in Table 6.3; they are also plotted as a function of $m_2$ in Fig. 6.2(b). By comparing Figs. 6.2(a) and 6.2(b) a good agreement can be found between the experimental separation performance and the position of the operating points with respect to the linear region of complete separation predicted by the triangle theory.

6.4 Application of the optimizing controller to a new separation

6.4.1 Setting up the on-line monitoring system

For a detailed description of the operation mode of the automated on-line HPLC monitoring system please refer to Section 4.3.3 in Chapter 4. Two main issues have to be addressed when tuning the on-line monitoring system for a new separation. On the one hand, at the beginning of a new cycle the HPLC needs to be ready for the next sample injection, hence, the time required for the HPLC analysis needs to be smaller than the cycle time of the SMB.
6.4 Application of the optimizing controller to a new separation

Figure 6.2: (a) Triangles of complete separation: linear triangle together with the position of the operating points 1 to 5 (dashed line); triangles for increasing feed concentration (solid lines). (b) Product purities vs. $m_2$ for runs 1 to 5. Dotted line indicates boundary of complete separation region.
6. Experimental implementation: Tröger’s Base separation

process. On the other hand, the time between the injection of two successive samples must be chosen long enough to avoid overlapping of the peaks. This is required to ensure baseline separation of the peaks and to allow for an accurate determination of the peak areas. Figure 6.3 shows a typical UV signal during the analysis of two successive samples.

The analytical column in the HPLC unit was tested in the same manner as the SMB columns, thus obtaining similar values for the Henry’s constants, namely $H_B = 2.050$ and $H_A = 5.303$, whilst the void fraction was determined to be $\epsilon^* = 0.708$. In the present case a good compromise between resolution of the peaks and retention time was found for a flow rate of 1.1 ml/min using pure ethanol as mobile phase and a waiting time of 8.25 min between two sample injections. Note that the mobile and stationary phases for the analysis in the HPLC and for the SMB unit do not necessarily have to be same. However, when using different solvents it should be taken into account that injecting a sample with a mobile phase composition different from the one used in the HPLC can generate additional solvent peaks that might interfere with the product peaks.

6.4.2 Controller

The only information about the system behavior required by the controller is the Henry’s constants of the two enantiomers to be separated and the average overall void fraction of the columns used in the SMB unit. Based on this information the controller’s code for the new separation task is built automatically as described elsewhere (Grossmann et al., 2008b).
6.4 Application of the optimizing controller to a new separation

Figure 6.3: Typical chromatogram of the two successive sample injections at a flow rate of 1.1 ml/min, recorded at a wavelength of 260 nm.
6. Experimental implementation: Tröger’s Base separation

6.5 Results and discussion

6.5.1 Set-point tracking at increasing feed concentrations

This part of the work has two main purposes, namely to demonstrate that the controller can be successfully applied under nonlinear chromatographic conditions, i.e. at high feed concentrations, and to compare the controller’s behavior when applied to the real plant and to a virtual plant, i.e. where the plant is substituted by a detailed SMB process simulator.

In a series of three experiments and five simulation runs increasing total feed concentration were considered, ranging from 0.75 to 16.0 g/L. The operating parameters of the different runs are reported in Table 6.4 in terms of initial $m_1$ values (same in all experiments), feed concentration, final $m_j$ values, and corresponding productivity. The latter is defined as:

$$PR = \frac{Q_F c_T^F}{n_{col} V(1 - \epsilon^*)} = \frac{(m_3 - m_2)c_T^F}{n_{col} t^*},$$  \hspace{1cm} (6.7)

where $Q_F$, $c_T^F$, $V$, and $n_{col}$ are the feed flow rate, the total feed concentration, the column volume, and the number of columns, respectively.

All experiments and simulations were carried out at a switch time of $t^* = 180$ s. The adsorption isotherm parameters used for the detailed simulations are those reported in Table 6.2, columns 4 and 5. For all the runs, the same minimal purity requirements were specified, namely 98.5% for both product streams. For the experiments the unit was always started up with clean columns, i.e. the unit was carefully flushed with pure solvent before every new experiment to remove any adsorbed component from the stationary phase material, and the lab temperature was kept constant at $T = 23^\circ$C.

Figures 6.4 to 6.6 show the evolution of the product purities as a function of the cycle number together with the trajectory of the operating conditions in the $(m_2, m_3)$ plane for the three runs A to C. In particular subfigures (a) and
Table 6.4: Start-up and final operating points for all controlled experiments together with the values of the productivity achieved at the final operating point. The switch time \( t^* = 180 \) s.

<table>
<thead>
<tr>
<th></th>
<th align="right">( m_1 )</th>
<th align="right">( m_2 )</th>
<th align="right">( m_3 )</th>
<th align="right">( m_4 )</th>
<th align="right">( c_F ) [g/L]</th>
<th align="right">( PR ) [g/(min L)]</th>
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</tbody>
</table>
Experimental implementation: Tröger’s Base separation

(b) show the results obtained for the experimental runs and for the simulations, respectively. Moreover, in the \((m_2, m_3)\) plane part of the boundaries of the corresponding triangle of complete separation, calculated for the Bi-Langmuir adsorption isotherm of Table 6.2, are drawn for the different total feed concentrations. For the sake of comparison in Fig. 6.2(a) the entire regions of complete separation for the different feed concentrations considered in this study are shown. For all three experiments and simulations the controller fulfills the product specifications within less than 40 process cycles, as it can be seen in Figs. 6.4 to 6.6.

The trajectories in the \((m_2, m_3)\) plane reflect the dynamic behavior of the controller: comparing the trajectories of experiment and simulation at a specific feed concentration, e.g. 4.0 g/L as shown in Fig. 6.5, reveals that the dynamic behavior of the experimental plant is well predicted by the detailed simulation. The same is true for the results obtained at 0.75 and 8.0 g/L, as shown in Figs. 6.4 and 6.6.

The final operating points reached by the controller, which correspond to the point of maximal productivity that can be achieved while guaranteeing the product specifications, are plotted using a different symbol in the \((m_2, m_3)\) plane of Figs. 6.4 to 6.6. Plotting both the final operating points and the triangles of complete separation for the different total feed concentrations together in the same Fig. 6.7 facilitates the comparison between experiments and simulations and allows to identify the trends observed for increasing feed concentrations. As to the position of the final operating points one can observe the same trend for the experiments and the simulations, namely with increasing feed concentration the final operating point shifts downwards to the left. This is in good agreement with the position of the vertices of the triangles of complete separation predicted by triangle theory for a Bi-Langmuir adsorption isotherm. Comparing simulations and experiments, it can readily be seen that in the case of 4.0 g/L the final operating points almost lie on top of each other, whereas in the other two cases the experimental points are shifted further downwards to the left. Considering run C, the difference in the
6.5 Results and discussion

![Graph showing purities of product streams and trajectory in the $(m_2, m_3)$ plane for $c_{F_T} = 0.75 \text{ g/L}$: (a) experiment; (b) simulation.](image)

Figure 6.4: Purities of the product streams as function of time measured in cycles together with the trajectory in the $(m_2, m_3)$ plane and the triangle of complete separation for $c_{F_T}=0.75 \text{ g/L}$: (a) experiment; (b) simulation.
Figure 6.5: Purities of the product streams as function of time measured in cycles together with the trajectory in the \((m_2, m_3)\) plane and the triangle of complete separation for \(c_T^{F}=4.0 \text{ g/L}\): (a) experiment; (b) simulation.
6.5 Results and discussion

Figure 6.6: Purities of the product streams as function of time measured in cycles together with the trajectory in the \((m_2, m_3)\) plane and the triangle of complete separation for \(c_{F,T}^E = 8.0\) g/L: (a) experiment; (b) simulation.
Figure 6.7: Position of the final operating points in the \((m_2, m_3)\) plane for runs A-E together with the triangles of complete separation calculated for a Bi-Langmuir isotherm.

The productivity values reported in Table 6.4 and calculated at steady state conditions using the final values for \(m_2\) and \(m_3\) increase with increasing total feed concentration from run A to E, as expected for a Bi-Langmuir type adsorption isotherm. Again, run C has not yet completely reached steady state conditions and the controller is still optimizing. We think this is the reason why for run C the final value of \(m_1\), reported in Table 6.4, is smaller than the average value of \(H_A\).
The experiments have shown that the optimizing controller is capable of fulfilling the process and product specifications for a separation problem governed by a Bi-Langmuir adsorption isotherm well into the nonlinear chromatographic regime even though it is based on the information about the linear adsorption behavior, only. Besides, we could demonstrate that the experimental and the simulated behaviors of the controller agree well in terms of both dynamic evolution and steady state operation even under nonlinear chromatographic conditions.

6.5.2 Disturbance rejection

Column overpressure

The very first experiment was carried out under the same conditions as reported in Table 6.4 for run A. After 28 cycles an unexpected loss of the extract purity occurred that should be viewed as a consequence of an unplanned, as yet unspecified disturbance. However, within 10 process cycles the controller rejected the disturbance and recovered the purity specifications, as shown in Fig. 6.8. During the last phase of this experiment from cycle 38 on, the controller reduced the step size and began to improve the separation performance of the unit by slowly increasing $m_3$, i.e. increasing the feed flow rate (see Fig. 6.8).

After the experiment the whole unit was carefully checked in order to investigate the unexpected behavior of the plant. The troubleshooting revealed that one of the columns started to leak and part of the stationary phase was washed out of the column, probably due to a damaged outlet frit. This incident caused blockage of the next column inlet and led to a steadily increasing pressure inside the unit, i.e. a disturbance unrelated to the monitoring system or to the controller. Figure 6.8 illustrates the pressure profile measured inside the column train for one of the columns as a function of the cycle number. The profile shows a clear increase starting at about cycle 25 and at the same
Figure 6.8: Purities of the product streams together with the pressure profile of one column as a function of time measured in cycles. Total feed concentration $c_F^T=0.75$ g/L: Extract (■); Raffinate (○); pressure profile (—). For the sake of clear representation, the trend of the pressure profile is indicated with a thick solid line.
Results and discussion

6.5 Results and discussion

time the extract purity started to decrease. Since this behavior of the unit was never observed before nor afterwards, we think that the leaking column and the ensuing pressure increase most likely led to the drop of the extract purity.

It has to be pointed out that the controller was of course unaware of this disturbance, and it only realized it by its effect on the product concentrations and purities. Nevertheless, the controller was able to recover the specified purities in a few cycles, and then to improve the process performance in terms of feed throughput. After this first experiment, the problem with the leaking column was fixed, and all the other experiments reported in this work (Section 6.5.1 and Section 6.5.2 ”Feed Pump malfunctioning”) were unaffected.

Figure 6.9: Trajectory of the operating conditions in the \((m_2, m_3)\) plane.

Feed Pump malfunctioning

The second disturbance was planned, and introduced, to simulate one of the common problems SMB practitioners experience, namely the malfunctioning
of a pump. In a SMB operation it is essential that the pumps deliver precise and constant flow rates over a long period of time to ensure the correct flows in the different sections of the SMB and to keep the unit at a constant operating point. However, in practice it is often observed that the actual flow rates of the pumps drift away from the set point implemented at the beginning of the operation. This can result in a loss of product purities. For the current case study, run C was disturbed by changing from cycle 75 the calibration factor of the feed pump. As a result and for the rest of the operation, the flow delivered by the feed pump to the SMB unit differed from the one dictated by the controller. Note that this disturbance was unknown to the controller and that the controller could only realize from the feedback information that purities were drifting away from the specified values.

More specifically, after cycle 75 the feed pump delivered 7.5% more flow than assigned by the controller, as shown in Fig. 6.10(b). It is important to understand qualitatively the effect of such a disturbance on the separation performance of the SMB unit. An increase of the feed flow rate results in an increase of the flow rates in sections 3 and 4, thus implying that the operating point is shifted upwards in the \((m_2, m_3)\) plane towards the region of pure extract resulting in a loss of raffinate purity as shown in Fig. 6.10(a). From cycle 80 on the purity was below the required specifications and dropped to a value of about 92%, but within less than 10 cycles the controller recovered the purity specifications. The disturbance rejection behavior of the controller reflects nicely its two main tasks. As soon as the controller realized that the raffinate purity did no longer meet the product specifications it reduced the flow rate in section 3 by reducing the feed flow rate to recover the raffinate purity as soon as possible (see Fig. 6.10(b)). Once the purities were back in the specifications the controller slowly increased the feed flow rate to improve the performance of the separation in terms of feed throughput. However, one can easily see from Fig. 6.10(b) that before and after the disturbance the controller did not yet attain steady state conditions but was still increasing the feed flow rate to improve the separation performance.
6.5 Results and discussion

Figure 6.10: Feed pump disturbance: (a) Product purities as a function of time measured in cycles. After 75 cycles the feed pump delivers 7.5% more flow than its set point. Total feed concentration $c_T^{F} = 8.0 \text{ g/L}$. (b) Feed flow rate as a function of time measured in cycles.
This result clearly demonstrates that the optimizing controller is able to efficiently reject pump disturbances and to improve the process in terms of feed throughput despite the occurrence of a feed pump disturbance.

6.6 Concluding remarks

In this Chapter, the experimental implementation of the 'cycle to cycle' control concept is presented for the separation of Tröger's Base enantiomers on CHIRALPAK™ AD using pure ethanol as mobile phase. It was demonstrated that the developed control concept is simple enough to be implemented quickly and reliably for a new separation campaign. In order to start the first control run three days of work had to be invested to set up the whole system for the new separation task. The three days were used for the following activities: one and a half days were needed to perform the system characterization, i.e. determining the void fraction and the Henry's constants for all nine chromatographic columns; one day to setup the monitoring system, i.e. tuning the injection procedure; half a day to develop the controller's code for the new separation.

In addition, a set of experimental runs was carried out to demonstrate the performance of the 'cycle to cycle' optimizing controller under nonlinear chromatographic conditions as well as to evaluate how the controller reacts to disturbances that are likely to occur during a separation campaign. The results presented in section 6.5.1 clearly demonstrate the most important feature of the controller, i.e. the capability to fulfill the product specifications and to improve the performance of the process with the knowledge of the linear adsorption behavior only, although the separation carried out is governed by a Bi-Langmuir type adsorption behavior. This is of great importance since the costly and time consuming task of determining the complete adsorption isotherm for a new separation problem becomes unnecessary. Furthermore, it was shown that the detailed simulations of the controller can well predict the dynamic and the steady state behavior of the actual plant under nonlin-
ear adsorption conditions. The results presented in section 6.5.2 show further that the controller successfully rejects unknown disturbances. The behavior of the controller is only affected by the feedback information from the plant, therefore, it is able to reject disturbances independently of their nature.

In summary, we can conclude that the ‘cycle to cycle’ optimizing controller and the approach presented in this work offer a fast and reliable way to set up new chiral SMB separations and to achieve optimal separation performance in a very short time.
6.7 Notations

\begin{itemize}
\item $c_i$ concentration of species $i$ [g/L]
\item $D_{ax,i}$ axial dispersion coefficient of component $i$ [cm$^2$/s]
\item $H_i$ Henry constants of species $i$ [-]
\item $k_{s,i}a_v$ mass transfer coefficient of component $i$ [1/s]
\item $K_{i,j}$ equilibrium constant of component $i$ with $(j = 1, 2)$ [L/g]
\item $m_j$ flow rate ratio in section $j$ [-]
\item $n_{col}$ number of columns [-]
\item $P$ purity [-]
\item $PR$ productivity [g/(min L)]
\item $Q_j$ volumetric fluid flow rate in section $j$ [ml/min]
\item $t^*$ switch time [min]
\item $t_0$ retention time of non-retained species [min]
\item $t_{R,i}$ retention time of component $i$ [min]
\item $V$ column volume [ml]
\item $V_j^D$ dead volume in section $j$ [ml]
\end{itemize}

Greek letters

\begin{itemize}
\item $\epsilon^*$ overall void fraction [-]
\item $\epsilon_b$ inter particle void fraction
\end{itemize}
6.7 Notations

Subscripts and superscripts

\[ A \] more retained component
\[ B \] less retained component
\[ \text{ave} \] average
\[ D \] desorbent
\[ E \] extract
\[ F \] feed
\[ i \] component index
\[ j \] section index, \((j = 1, \ldots, 4)\)
\[ R \] raffinate
6. Experimental implementation: Tröger’s Base separation
Chapter 7

Modified SMB scheme: Intermittent simulated moving bed I-SMB

7.1 Introduction

The application of SMB units for chiral separations has increased over the last years because of their better performance as compared to batch chromatography and the fact that SMB units can be easily scaled up from drug development scale to industrial production scale. Nevertheless, there has been continuous effort to develop modified SMB schemes to improve the separation performance yet guaranteeing the specified product purities. The different proposed concepts can be classified into two main groups, namely modifications in the operation mode of the classical SMB or implementation of new multi-column process schemes. Some of the suggested new operation modes are listed in
the following: PowerFeed, where the feed flow rate is varied during a switch period (Zhang et al., 2003, 2004); ModiCon where the feed concentration is modulated within a switch (Schramm et al., 2002, 2003c,b); enriched extract SMB (EE-SMB) where part of the extract stream is continuously concentrated before being re-injected to Section 2 of the SMB (Bailly et al., 2004; Paredes et al., 2006).

In chiral chromatography the costs for the stationary phase material make up a significant portion of the total production costs. For this reason, there is a lot of interest in new multi-column process schemes that allow to increase the feed throughput per volume of stationary phase material. Introducing the concept of partial feed and partial withdrawal, which allows to change the internal flow rates during the switch period, was an important step in the direction of new process schemes and was first presented by (Kearney and Hieb, 1992; Kloppenburg and Gilles, 1999b). This concept has been well studied by Wankat and his coworkers and they have introduced the partial feed operation, where the feed is only introduced for a fraction of the switch period (Zang and Wankat, 2002a). In a further publication they have extended the concept to a three zone SMB with partial feed and partial withdrawal (Zang and Wankat, 2002b). More recently this group has developed a semicontinuous two-zone SMB/chromatography hybrid system for ternary separations (Hur and Wankat, 2005, 2006). A special case of the partial feed and partial withdrawal process is patented and commercialized by the Nippon Rensui company the so-called improved SMB (I-SMB) process (Tanimura et al., 1995). In this process the switch time is divided into two phases; in the first phase the unit is operated as a conventional SMB, however, no flow in section 4 and in the second phase all inlet and outlet ports are closed and the fluid is just circulated in the column train. This Chapter presents the principle of the I-SMB and reports and discusses the first experimental implementation to chiral separations.
7.2 I-SMB chromatography

7.2.1 Principle of the I-SMB

Figure 7.1 shows a schematic of the closed loop I-SMB process, where a series of four columns is divided into four zones by two inlet (Feed, Desorbent) and two outlet ports (Extract, Raffinate). Periodically, the port locations are switched in the direction of the fluid flow to simulate in a discrete manner a continuous counter-current movement of the fluid phase with respect to the stationary phase. The time interval between two successive port switches is referred to as switch time, $t^*$. In contrast to the operation of a conventional SMB unit the switch time is divided into two sub-intervals, step I and step II, as illustrated in Fig. 7.1(a). In the first interval with duration $\alpha t^*$ (step I), the unit is operated as a conventional SMB, with two inlet streams (Feed, Desorbent) and two outlet streams (Extract, Raffinate), however, no flow in section 4. In step II with duration $\beta t^*(\beta = 1 - \alpha)$, 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. Consequently, the flow rate in step II is the same in all four sections and it is called $Q_4$. The corresponding flow rates in section 1, 2, and 3 during step I are called $Q_1$, $Q_2$, and $Q_3$, respectively.

7.2.2 Triangle Theory for I-SMB

In the frame of the equilibrium theory, where local equilibrium is assumed between the fluid and solid phase and axial dispersion is neglected, one can develop constraints for complete separation for the I-SMB similar to the SMB (Mazzotti et al., 1997; Migliorini et al., 1999b; Rajendran et al., 2009;
7. Modified SMB scheme: Intermittent simulated moving bed I-SMB

(a) Time sequence of I-SMB.

(b) I-SMB unit configuration in step I.

(c) I-SMB unit configuration in step II.

Figure 7.1: Scheme of the I-SMB process: (a) timeline; (b) operation mode during step I; (c) operation mode during step II. Port switching takes place at the end of step II and the beginning of step I.
Let us consider a linear adsorption isotherm

\[ n_i^* = H_i c_i \quad (i = A, B), \]

\[ H_A > H_B, \]

where \( H_i \) is the Henry constant of component \( i \), \( c_i \) and \( n_i^* \) are the concentration of component \( i \) in the liquid phase and the concentration in the solid phase in equilibrium with the liquid, respectively. Then the retention time of component \( i \) in section \( j \) of the I-SMB unit can be calculated according to Eq. 7.2.

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

In above equation \( V \), \( \epsilon^* \), and \( \hat{Q}_j \) are the volume of the column, the average overall void fraction of the columns, and the flow rate in section \( j \) averaged over one switch period, respectively. The latter is given as:

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

The constraint for complete separation can be derived in the same way as for the conventional SMB, namely considering the specific task every section has to fulfill within the I-SMB operation. In section 2 and 3 the separation takes place and in section 1 and 4 the stationary and the mobile phase need to be regenerated, respectively. The operation conditions in section 2 have to be chosen in such a way that the retention time of component \( B \) in section 2 is smaller than the switch time, whereas the retention time of component \( A \) needs to be larger. This operation mode ensures that component \( A \) can be collected at the extract port and component \( B \) is completely removed from the column before the next port switch and does not contaminate the extract. The operation in section 3 can be designed in a similar way. The switch time needs to be larger than the residence time of component \( B \) in section 3 but smaller
than that of component A. In section 1 the stationary phase material needs to be regenerated, therefore, the switch time \( t^* \) needs to be larger than the residence time of component A in section 1. This assures that component A is completely eluted from the column before the next port switch. In the case of a closed loop operation the fluid phase needs to be regenerated in section 4 before being fed back to section 1. This constraint is fulfilled if the switch time is smaller than the residence time of component B in section 4. The above discussion can be summarized to yield the following set of constraints:

\[
\begin{align*}
\text{Section 1:} & \quad t_{A,1}^r \leq t^*, \\
\text{Section 2:} & \quad t_{B,2}^r \leq t^* \leq t_{A,2}^r, \\
\text{Section 3:} & \quad t_{B,3}^r \leq t^* \leq t_{A,3}^r, \\
\text{Section 4:} & \quad t^* \leq t_{B,4}^r.
\end{align*}
\tag{7.4}
\]

As it is done for the conventional SMB, one can define the average flow rate ratio \( m_j \) for the I-SMB process using the averaged flow rate \( \hat{Q}_j \):

\[
m_j = \frac{\hat{Q}_j t^* - V e^*}{V (1 - e^*)} \quad (j = 1, \ldots, 4).
\tag{7.5}
\]

Combining Eq. 7.2 with inequalities 7.4 and applying Eq. 7.5 yields the following criteria for the choice of the flow rate ratios \( m_j \) which if fulfilled lead to complete separation:

\[
\begin{align*}
H_A \leq m_1, \\
H_B \leq m_2 \leq H_A, \\
H_B \leq m_3 \leq H_A, \\
m_4 \leq H_B.
\end{align*}
\tag{7.6}
\]

This result reveals that for linear adsorption conditions the I-SMB separation can be designed applying the same criteria on the choice of the flow rate ratios \( m_j \) as for the conventional SMB (see inequalities 2.14).
7.2 I-SMB chromatography

7.2.3 Design of the I-SMB process

Dividing the switch time into two sub-intervals introduces a further degree of freedom for the operation of the I-SMB compared to the conventional SMB. Therefore, the I-SMB process in total offers six degrees of freedom; the four flow rates \( Q_j (j = 1, \ldots, 4) \), the switch time \( t^* \), and the parameter \( \alpha \) which defines the duration of the two sub-intervals. The corresponding six constraints have recently been discussed (Katsuo and Mazzotti, 2009)

Two such constraints stem from the specification on the maximum allowable pressure drop through the sequence of I-SMB columns, \( \Delta P_{\text{max}} \), which is a consequence of the fact that chiral stationary phases exhibit high efficiency, hence the fluid velocity is upper bounded by pressure drop rather than by efficiency considerations. In general the pressure drop along one column can be calculated applying Darcy's law:

\[
\frac{\Delta P_j}{L} = \frac{\phi Q_j}{A_{\text{col}}},
\]

where \( \Delta P_j \), \( L \), and \( A_{\text{col}} \) are the pressure drop of one column in section \( j \), the column length, and the cross-section, respectively. The parameter \( \phi \) depends on the properties of the stationary phase material as well as on the properties of the mobile phase used for the separation. Since the flow rates differ in the different sections of the I-SMB, the total pressure drop along the unit is calculated summing up the pressure drops of the different sections.

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

In above equation \( n_j \) is the number of columns present in section \( j \). As already mentioned, the switch period in the I-SMB process is divided in two sub-intervals with different modes of operation, however, the pressure drop constraint needs to be fulfilled in both cases leading to the following set of
inequalities:

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

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

(7.9)

To avoid unnecessary pressure fluctuations between step I and II, it is additionally enforced that \(\Delta P_I = \Delta P_{II} = \Delta P_{\text{max}}\). This condition together with the constraint on the maximum allowable pressure drop and a set of four \(m_j\) values allows to calculate the minimum switch time \(t^*\), the parameter \(\alpha\), and the four flow rates \(Q_j\). Applying Eqs. 7.5, 7.7 and 7.9 leads to the following equations for \(t^*\) and \(\alpha\):

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

(7.10)

\[
\alpha = \frac{\sum_{j=1}^{3} n_j (m_j - m_4)(1 - \epsilon^*)}{\sum_{j=1}^{4} n_j (m_j(1 - \epsilon^*) + \epsilon^*)}. \tag{7.11}
\]

It can readily be observed that the minimum switch time \(t^*\) and the parameter \(\alpha\) are independent of each other. In Chapter 2 it has been presented that in small scale SMB units the extra-column dead volume has to be taken into account in the design of the operation conditions to guarantee satisfying separation results. The same is true for the I-SMB process and similar to the SMB unit the definition for the flow rate ratios for an I-SMB unit with considerable extra-column dead volume is given as:

\[
m_j = \frac{\dot{Q}_j t^* - V \epsilon^* - V_j^D}{V(1 - \epsilon^*)} \quad (j = 1, \ldots, 4), \tag{7.12}
\]

where \(V_j^D\) is the extra-column dead volume in section \(j\). Consequently,
Eqs. 7.10 and 7.11 have to be recalculated applying Eq. 7.12:

\[ t^* = \frac{\phi L^2}{\Delta P_{\text{max}}} \sum_{j=1}^{4} n_j \left( m_j (1 - \epsilon^*) + \epsilon^* + \frac{V_j^D}{V} \right), \quad (7.13) \]

\[ \alpha = \frac{\sum_{j=1}^{3} n_j (m_j - m_4) (1 - \epsilon^*)}{\sum_{j=1}^{4} n_j \left( m_j (1 - \epsilon^*) + \epsilon^* + \frac{V_j^D}{V} \right)}. \quad (7.14) \]

Comparing Eq. 1.13 with Eq. 7.10, it becomes clear that for a given SMB and I-SMB unit having the same geometric configuration and applying the same design criteria in terms of pressure drop and average flow rate ratios, the switch time \( t^* \) and the average flow rates in the different sections are identical; hence both units achieve the same throughput. This fact allows for an easy comparison between I-SMB and the conventional SMB unit.

### 7.2.4 Cyclic steady state analysis

This section aims at comparing the conventional SMB and the I-SMB, both in the 1-1-1-1 configuration, in terms of their productivity, i.e. the amount of component separated per unit time and per unit volume of stationary phase material. From the previous section it is known that for a given set of flow rate ratios and applying the same pressure drop constraint both units achieve the same throughput. However, the same throughput for two different units only corresponds to the same productivity if both units use the same amount of stationary phase material and achieve the same product purities. To compare the two processes, we will carry out a case study at linear adsorption conditions for the separation of a racemic mixture of an Allene, the same compound that was separated in the work presented in Chapter 2, and the system parameters are listed in Table 7.1.

For a fixed value \( t^* \), the point that maximizes throughput and achieves complete separation is the vertex of the triangle of complete separation where \( m_2 \)...
7. Modified SMB scheme: Intermittent simulated moving bed I-SMB

Table 7.1: Column and system parameters.

<table>
<thead>
<tr>
<th>Column</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>$S$ (cm$^2$)</td>
<td>0.166</td>
</tr>
<tr>
<td>$L$ (cm)</td>
<td>15.0</td>
</tr>
<tr>
<td>$\epsilon^*$ (-)</td>
<td>0.63</td>
</tr>
<tr>
<td>$\Delta P_{\text{max}}$ (bar)</td>
<td>40</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>System Characteristics</th>
<th>Component A</th>
<th>Component B</th>
</tr>
</thead>
<tbody>
<tr>
<td>$H_i$ (-)</td>
<td>3.18</td>
<td>1.66</td>
</tr>
<tr>
<td>$k_{s,i}a_v$ (1/sec)</td>
<td>1.82</td>
<td>2.70</td>
</tr>
<tr>
<td>$\frac{b_D ax,i}{u}$ (m)</td>
<td>$2.21 \times 10^{-5}$</td>
<td></td>
</tr>
<tr>
<td>$\phi$ (bar min/cm$^2$) c</td>
<td>0.0196</td>
<td></td>
</tr>
</tbody>
</table>

and $m_3$ are as small and as large as possible, i.e. $Q_F = Q_3 - Q_2$ is maximized (see point O in Fig. 7.2). The region of complete separation for the Allene separation was obtained assuming columns with infinite efficiency, which is not realistic for real columns, due to the presence of axial dispersion and mass transfer resistance. Therefore, close to the vertex, the separation does not reach high product purities especially for a conventional four column SMB in the 1-1-1-1 configuration. For this reason SMB units are normally operated with 6 (1-2-2-1) or 8 (2-2-2-2) columns to overcome the limitation on the product purities. In the patent of the I-SMB process, however, it is stated that the four column I-SMB process is not affected by such purity limitations (Tanimura et al., 1995).

To address this issue the two processes are compared carrying out a cyclic steady state analysis using the equilibrium theory model (see Section 1.3), where axial dispersion and mass transfer resistance are neglected. The operating points labeled with N, O, and P were chosen for the cyclic steady state analysis. The position of the operating points in the $(m_2, m_3)$ plane is shown
Figure 7.2: Linear region of complete separation and regeneration for the Allene separation. Open symbols show the position of the operating points that were chosen for the cyclic steady-state analysis. The values of $m_1$, $m_4$, $t^*$, and $\alpha$ are the same for all cases.
7. Modified SMB scheme: Intermittent simulated moving bed I-SMB

in Fig. 7.2; N and P are outside and inside the region of complete separation, respectively, and O is on the vertex of the triangle.

Applying the methods of characteristics to solve the equilibrium theory model for linear adsorption conditions \( n_i^* = H_i c_i \) one obtains the velocity at which component \( i \) in solution travels along the column (Rhee et al., 2001), i.e.

\[
v_i = \frac{u_j}{\epsilon^* + (1 - \epsilon^*) H_i}. \tag{7.15}
\]

The exact operating parameters in terms of flow rate ratios \( m_j \), switch time \( t^* \), step ratio \( \alpha \), flow rates \( Q_j \), and the purity values are reported in Table 7.2. The purity values were obtained from detailed simulations. For the calculations the equilibrium dispersive model is used as presented in Chapter 2 and the model parameters are reported in Table 7.1.

Conventional SMB (1-1-1-1)

Let us first consider the conventional SMB and the operating point at the vertex of the triangle indicated with O. The cyclic steady state behavior of the unit for this operating point can be illustrated in a time-space diagram as shown in Fig. 7.3(b). The space axis (x-axis) is divided into four sections each of which corresponding to one column and the position of the inlet ports (Feed F, Desorbent D) and the outlet ports (Extract E, Raffinate R) is indicated below the axis. The y-axis represents the time and scales from 0 to the switch time \( t^* \). The fluid flow is from left to right and after each switch period, \( t^* \), the inlet and outlet ports are shifted one position to the right which corresponds to one column. The solid and the dashed lines delimit the position of the more (A) and the less retained (B) component in the unit, respectively. For both components the position of the concentration front and of the concentration tail is indicated. The slopes of the tails and fronts of component A and B are the reciprocals of the corresponding propagation velocities calculated according to Eq. 7.15. Between the fronts of component B and A only component B is present, whereas between the front of A and the tail of B both components
Table 7.2: Operating parameters and purity performance of the simulated SMB and I-SMB runs (1-1-1-1 configuration).

<table>
<thead>
<tr>
<th>Operating mode</th>
<th>Point</th>
<th>Flow rate ratio</th>
<th>( t^* ) (sec)</th>
<th>Flow rate (mL/min)</th>
<th>Purity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>( m_1 )</td>
<td>( m_2 )</td>
<td>( m_3 )</td>
<td>( m_4 )</td>
</tr>
<tr>
<td>SMB</td>
<td>P</td>
<td>3.82</td>
<td>1.96</td>
<td>2.88</td>
<td>1.33</td>
</tr>
<tr>
<td></td>
<td>O</td>
<td>3.82</td>
<td>1.66</td>
<td>3.18</td>
<td>1.33</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>3.82</td>
<td>1.36</td>
<td>3.48</td>
<td>1.33</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>
</tr>
<tr>
<td></td>
<td>O</td>
<td>3.82</td>
<td>1.66</td>
<td>3.18</td>
<td>1.33</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>3.82</td>
<td>1.36</td>
<td>3.48</td>
<td>1.33</td>
</tr>
</tbody>
</table>
are present, and between the tails of B and A only component A is present.

From Fig. 7.3(b), it can be seen that the front of component A connects the feed port with the raffinate port and the tail of component B connects the extract port with the feed port within one switch period. This observation implies that the residence time of component A in column 3 and the one of component B in column 2 is equal to the switch time $t^*$, i.e. $t_{rA,3}^r = t^*$ and $t_{rB,2}^r = t^*$.

Consequently, $m_3 = H_A$ and $m_2 = H_B$ which corresponds to the vertex of the triangle of complete separation and is in agreement with the selection of operating point O. The operating conditions in section 1 and 4 were chosen so as to guarantee complete regeneration of the stationary phase and of the mobile phase, respectively. As a consequence, the tail of component A leaves column 1 before the end of the switch period and the front of component B does not reach the end of column 4 within the switch period. To summarize under these process conditions both product streams extract and raffinate can be collected pure. However, this is only true if the assumption of infinite column efficiency underlying the above analysis is valid. Any deviation from the equilibrium theory due to the presence of mass transfer resistance or axial dispersion would result in polluted product streams. This can easily be understood considering the position of the front of component A at the end of the switch period (see Fig. 7.3(b)), which is exactly before the raffinate port and the presence of axial dispersion would immediately cause pollution of the raffinate stream. The same is true for the tail of component B any deviation from ideality would result in a polluted extract stream.

Figure 7.3(a) reports the result for the cyclic steady state analysis of operating point P which is located inside the region of complete separation. It can readily be seen that also in this case both product streams are collected pure since $t_{rA,3}^r > t^*$ and $t_{rB,2}^r < t^*$. This time, however, the presence of axial dispersion or mass transfer resistance would not necessarily result in a pollution of the product streams since the front of component A does not reach the raffinate port within the switch period and the tail of component B is eluted from column 2 before the end of the switch period.
Figure 7.3(c) shows the cyclic steady state behavior of the conventional SMB for the operating point N, i.e. outside the region of complete separation. As expected from the position of the operating point in the $(m_2, m_3)$ plane both extract and raffinate are polluted, i.e. $t_{A,3}^* < t^*$ and $t_{B,2}^* > t^*$

**I-SMB (1-1-1-1)**

The cyclic steady state behavior of the I-SMB unit is illustrated in Figs. 7.3(d), (e), and (f) corresponding to the operating points P, O, and N, respectively. Let us first discuss the differences in the time-space diagram between the conventional SMB and the I-SMB process. During step I of the I-SMB process there is no flow in section 4, hence the fronts can not propagate into section 4. In step II, the flow rate is the same in all four sections of the I-SMB unit as a result the front and the tail of one component have the same slope in all columns.

Figure 7.3(e) reports the results for the cyclic steady state behavior of the I-SMB for the operating point O and as in the case of the SMB the front of A connects the feed port to the raffinate port within the switch period $t^*$ (see Fig. 7.3(b)). However, in contrast to the SMB operation the raffinate stream is only collected until $\alpha t^*$ where the front of A is still well separated from the raffinate port as can be seen in Fig. 7.3(e). A similar analysis can be carried out for component B revealing that the tail of B is eluted from column 2 long before the next port switch occurs (see Fig. 7.3(e)). Comparing Fig. 7.3(e) with Fig. 7.3(b), it is apparent that the region in the column train where both components are present, i.e. between the front of A and the tail of B, is much smaller for the I-SMB. This is an important observation and a key result. Therefore, we can conclude that even if an I-SMB unit is operated at the vertex of the region of complete separation, the position of the front of A and the tail of B is such that the presence of non ideal effects such as axial dispersion and mass transfer resistance do not necessarily cause pollution of the product streams.
7. Modified SMB scheme: Intermittent simulated moving bed I-SMB

Figure 7.3: Equilibrium theory cyclic steady-state solutions of conventional 4-column SMB and I-SMB processes. (a) SMB; point P. (b) SMB; point O. (c) SMB; point N. (d) I-SMB; point P. (e) I-SMB; point O. (f) I-SMB; point N.
For operating point P which is located inside the complete separation region the same effect is observed (see Fig. 7.3(d)). Finally, Fig. 7.3(f) shows the results for the operating point N outside the triangle of complete separation and it is apparent that the region where both components are present has increased since the front of A and the tail of B were moved to the right and left, respectively. Thus, the two product streams extract and raffinate are no longer obtained pure.

These results demonstrate that the I-SMB process can achieve higher productivity than the conventional SMB since for a given purity specification the 1-1-1-1 I-SMB can be operated closer to the vertex of the triangle, i.e. maximizing $Q_F = Q_3 - Q_2$, than the conventional SMB in the 1-1-1-1 configuration. To realize high purities close to the vertex of the triangle a SMB unit would have to be operated in the 1-2-2-1 configuration which reduces the productivity since the amount of required stationary phase material increases.

The above results have been confirmed carrying out detailed simulations using an equilibrium dispersive model and the results are presented in following publication (Katsuo and Mazzotti, 2009).

### 7.3 Experimental implementation of the I-SMB: Triol separation

#### 7.3.1 Experimental setup

The experimental setup is based on an ÄKTA™ explorer 100 system (GE Healthcare) and all devices such as pumps and multi-position valves are controlled by the UNICRON™ software provided by GE Healthcare (Katsuo et al., 2009b; Abel et al., 2004a). Our laboratory SMB unit was set up according to the geometric configuration shown in Fig. 7.4. The prepacked analytical columns (15 cm × 0.46 cm) are connected in series and the inlet and outlet
manifolds are connected to multi-position valves to realize the periodic switching of the ports. In between two consecutive columns a check valve is placed to prevent fluid flow in reverse direction. To account for the effect of extra-column dead volume the volume of the different tubing parts and manifolds connecting two columns was determined. The similarity in the experimental implementation of the SMB and the I-SMB process allows to use the same unit to carry out both process configurations. For the I-SMB process the raffinate pump, required in the SMB configuration, is just replaced with an on/off valve. All the experiments were carried out using the I-SMB in the 1-1-1-1 column configuration, i.e. one column per section.

Figure 7.4: Scheme of the laboratory I-SMB unit.
7.3.2 Materials and Characterization

In this work, we consider the compound 2-(2,4-difluorophenyl)butane-1,2,3-triol, which exhibits two chiral centers, hence it has four different forms, namely (R,R), (S,S), (R,S) and (S,R). This is an important intermediate for the preparation of different types of antifungal drugs. Synthesis, as described elsewhere (Acetti et al., 2009), leads to the racemic mixture rac-(RS,RS)-2-(2,4-difluorophenyl)butane-1,2,3-triol consisting only of the (R,R)- and the (S,S)-enantiomer, which are shown in Fig. 7.5. For further use in the laboratory the racemic mixture is separated in its pure enantiomers using the I-SMB technology. The separation is carried out on CHIRALPAK™ AD (Chiral Technologies Europe, Illkirch, France) using a mixture of hexane/methanol/ethanol 60/20/20 vol% as mobile phase. The experiments were all carried out at room temperature, i.e. 22±1 °C.

![Figure 7.5: (RS,RS)-2-(2,4-difluorophenyl)butane-1,2,3-triol (triol).](image)

The overall void fraction of the columns installed in the I-SMB unit was determined injecting pulses of 1,3,5-Tris-tert-butylbenzene (TTBB) (Fluka, Buchs, Switzerland) which is considered to be non retained. For the determination of the hold-up time \( t_0 \) the residence time of TTBB has to be corrected with the dead time of the HPLC unit. The overall void fraction \( \epsilon^* \) of the columns is then calculated as follows:

\[
\epsilon^* = \frac{t_0 Q}{V}
\]
The Henry constants of the two enantiomers were calculated from the retention times obtained from pulse injection experiments carried out at diluted conditions, i.e.

\[ H_i = \frac{\epsilon^*}{1-\epsilon^*} \left( \frac{t_{R,i} - t_0}{t_0} \right) \quad (i = A, B). \]  

(7.17)

In the equation above \( t_{R,i} \) is the residence time of component \( i \) corrected with the dead time of the HPLC.

The pressure drop factor \( \phi \) was experimentally determined measuring the pressure drop in the HPLC with and without the column being installed. The difference of the two values is the pressure drop along the column. This procedure was repeated at two different flow rates and the obtained results together with the origin were linearly regressed according to Darcy’s law (see Eq. 7.7).

Due to the limited amount of material available, in this work the nonlinear adsorption isotherm was estimated based only on a limited number of experiments. Four overloaded pulse chromatograms were measured using the racemic mixture at different injection volumes with a concentration of 15 g/L at 22 °C, as shown in Fig. 7.6.

It is rather obvious that the nonlinear chromatographic regime has been reached and that both enantiomers exhibit a Langmuir-like behavior. Therefore, the competitive binary Langmuir isotherm

\[ n_i = \frac{N_i K_i c_i}{1 + K_{CA} c_A + K_{CB} c_B}, \]

(7.18)

was used to describe the adsorption behavior of the two components. Equation 7.18 is regarded accurate enough to choose the operating conditions for the I-SMB experiments. The adsorption isotherm parameters were estimated by fitting the experimental profiles to simulations results obtained with an equilibrium dispersive model of the chromatographic column. The quality of fitting is illustrated in Fig. 7.7 for one of the experiments, and the values of
7.3 Experimental implementation of the I-SMB: Triol separation

Figure 7.6: Overloaded pulse injection experiments with increasing injection volume at 15 g/L.
The difference between the values of the Henry constants measured through analytical injections in the linear regime and those estimated considering overloaded chromatograms and the binary Langmuir isotherm is rather small (see Table 7.3), i.e. less than 1%. It is worth mentioning that the adsorption isotherm that has been measured and adopted to design the I-SMB experiments has a limited accuracy, but is good enough to assign the SMB design criteria, what it is meant for.

![Figure 7.7: Comparison between the experimental (dashed line) and the simulated (solid line) chromatograms for an injection volume of 60 \( \mu L \).](image)

### 7.3.3 Results and discussion

This section presents the results about the successful I-SMB separation of a racemic mixture of the compound (RS,RS)-2-(2,4-difluorophenyl)butane-1,2,3-
triol into its pure enantiomers, for further use. The minimal purity specification for further use for both enantiomers is 98%. In a series of eleven experiments increasing total feed concentrations (from 3 to 15 g/L) have been considered, as that improves productivity and throughput. This is true for both SMB and I-SMB operations due to the analogy of the two processes (Katsuo and Mazzotti, 2009).

The experiments are labeled A to K and the position of the different operating points in the \((m_2, m_3)\) plane are indicated in Figs. 7.8(a) to (d): A to C are carried out at a total feed concentration of 3 g/L, D and E at 6.5 g/L, F and G at 10 g/L, and H to K at 15 g/L. In the same figures the complete separation regions corresponding to the different feed concentrations are also drawn. These were obtained using the isotherm parameters determined in the previous section and applying the equations presented earlier (Mazzotti et al., 1997; Katsuo and Mazzotti, 2009; Katsuo et al., 2009a). The I-SMB was always...
7. Modified SMB scheme: Intermittent simulated moving bed I-SMB

started up with clean columns, i.e. the unit was carefully flushed with mobile phase between two successive experiments to remove any adsorbed component that remained on the stationary phase from the previous experiment. The exact operating parameters in terms of flow rates $Q_j$, flow rate ratios $m_j$, switch time $t^*$, and step ratio $\alpha$ are listed in Table 7.4. For all the experiments carried out $m_1$ and $m_4$ were chosen so as to guarantee complete regeneration of the stationary phase in section 1 and of the mobile phase in section 4, respectively. The corresponding values are also listed in Table 7.4.

In order to determine the cyclic steady state of the operation one keeps track of the concentration evolution of both enantiomers in the two product streams. Therefore, the outlet streams were collected in small glass flasks over one cycle and then analyzed in a HPLC unit. The cyclic steady state is reached when the peak areas, obtained from HPLC analysis, of the two enantiomers in both product streams differ by less than a few percentage points for a few cycles. Based on the experimental evidence and the general features of SMB separations all experiments were continued for at least 14 cycles to attain steady state conditions. The results of the HPLC analysis at steady state were used to calculate the purities ($P_{\text{ext}}$, $P_{\text{raf}}$) in the two product streams (see Table 7.4) according to the following equation:

\[
P_{\text{ext}} = 100 \frac{A_A^{\text{ext}}}{A_A^{\text{ext}} + A_B^{\text{ext}}} \quad \text{and,} \quad P_{\text{raf}} = 100 \frac{A_B^{\text{raf}}}{A_A^{\text{raf}} + A_B^{\text{raf}}},
\]

(7.19)

where $A_i^{\text{raf}}$ and $A_i^{\text{ext}}$ correspond to the peak area of component $i$ in the extract and the raffinate stream, respectively. Note that in the calculation of the purities the presence of the weakly retained impurity is neglected and Eq. 7.19 is correct if the UV absorbance of component A and B is the same, which is a reasonable assumption for two enantiomers.

In Figs. 7.8(a) to 7.8(d), the position of the operating points in the $(m_2, m_3)$
The productivity PR at steady state is calculated as: $PR = \alpha (Q3 - Q2)c_F$.

<table>
<thead>
<tr>
<th>Run</th>
<th>Run</th>
<th>$c_F$ [g/L]</th>
<th>$Q_1$ [mL/min]</th>
<th>$Q_2$ [mL/min]</th>
<th>$Q_3$ [mL/min]</th>
<th>$Q_4$ [mL/min]</th>
<th>$t^*$ [min]</th>
<th>$\alpha$</th>
<th>$m_1$</th>
<th>$m_2$</th>
<th>$m_3$</th>
<th>$m_4$</th>
<th>$P_{ext}$ [%]</th>
<th>$P_{raf}$ [%]</th>
<th>$PR$ [mg/min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>3</td>
<td>3.02</td>
<td>1.21</td>
<td>1.61</td>
<td>1.46</td>
<td>2.11</td>
<td>0.4</td>
<td>2.2</td>
<td>1.3</td>
<td>1.5</td>
<td>0.7</td>
<td>99</td>
<td>99.6</td>
<td>0.48</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>3</td>
<td>2.87</td>
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plane is shown together with the regions of complete separation for the different feed concentrations. In the same figures the linear triangle of complete separation is drawn in dashed lines. The effect of feed concentration on the shape and size of the triangle of complete separation becomes most evident when comparing Fig. 7.8(a) with Fig. 7.8(d). As expected from triangle theory for a system characterized by Langmuirian adsorption behavior, the region of complete separation shrinks, bends downwards to the left and the triangle becomes more and more distorted for increasing feed concentration (Mazzotti et al., 1997). Consequently, when choosing the operating conditions for the I-SMB experiments, in terms of the flow rate ratios $m_2$ and $m_3$, one has to account for the shift of the triangle of complete separation by changing the values of $m_2$ and $m_3$ accordingly (see Table 7.4).

With the exception of run K all the operating points were chosen to be inside the region of complete separation or at least on the boundary as in the case of run A. The obtained purity values reported in Table 7.4 are reasonably in line with the predictions from triangle theory in particular if considering the fact that the adsorption isotherm has only been estimated. To evaluate the accuracy of the estimated regions of complete separation it would have been necessary to choose operating points outside the complete separation region to be able to determine the position of the boundaries. However, this would have been contradictory to the objective of this work, i.e. to produce the two enantiomers with the requested purity specifications.

Considering the obtained purity results two exceptions were observed from the predicted trend of the triangle theory, namely run K and I (see Table 7.4). In the former case the purity specifications were fulfilled even though the operating point lies outside the boundary of complete separation. For run I, the opposite is the case, the purity specifications are not fulfilled, namely $P_{ext}$ 96.5%, $P_{raf}$ 99.3%, but the operating point lies inside the predicted region of complete separation. Yet this result is not surprising considering the fact that the isotherm was only estimated and not carefully characterized as it would be necessary to obtain the exact regions of complete separation.
7.3 Experimental implementation of the I-SMB: Triol separation

Figure 7.8: Position of the operating points in the \((m_2, m_3)\) plane for runs A to K: (a) A to C 3 g/L; (b) D and E 6.5 g/L; (c) F and G 10 g/L; (d) H to K 15 g/L.
7.3.4 Concluding remarks

In this Section the chromatographic separation of the racemic mixture (RS,RS)-2-(2,4-difluorophenyl)butane-1,2,3-triol into its pure enantiomers was performed using an I-SMB process. This is a new technology that has been demonstrated recently (Katsuo and Mazzotti, 2009; Katsuo et al., 2009a) and is applied here for the first time to the separation of the enantiomers of a non-commercial chiral compound at rather high feed concentration, i.e. up to a total feed concentration of 15 g/L. The first objective in this work was to present the different steps required to set up a successful I-SMB separation to obtain the two enantiomers with the requested purity specifications if only a limited amount of material is available. The second objective aimed at illustrating the effect of feed concentration on the choice of the operating parameters. Therefore, we have performed experiments at increasing total feed concentration ranging from 3 to 15 g/L, as can be seen in Table 7.4. For all experiments the specified purity specification of 98% for both product streams extract and raffinate could be achieved except for run I. The I-SMB process could be successfully applied quantitatively and at the end of the project 4.5 g of the racemic mixture could be separated with the given purity specification. The fact that we could obtain in-spec products is a demonstration of the quality of the prediction capability of the design tools that we have used to set up the I-SMB separation. In conclusion, the current work demonstrates that I-SMB can be successfully applied to the separation of chiral intermediates or final pharmaceutical products.
7.4 Nomenclature

$A$ Area of the chromatogram
$A_{\text{col}}$ cross-sectional area of the column
$c_i$ fluid phase concentration of component $i$
$D_{\text{ax},i}$ axial dispersion coefficient of component $i$
$H_i$ Henry constant of component $i$
$k_{s,i}a_v$ mass transfer coefficient of component $i$
$K_i$ equilibrium constant of component $i$
$L$ column length
$m_j$ flow rate ratio in section $j$
$n_i^*$ 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 $j$
$S$ selectivity
$t^*$ switch time
$t_{i,j}^s$ retention time of component $i$ in section $j$
$u_j$ superficial velocity in section $j$
$v_i$ 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
$\phi$ pressure drop coefficient in Eq. 7.7
Subscripts and Superscripts

$A$ component A  
$B$ component B  
$ext$ Extract  
$i$ component index  
$j$ section index  
$raf$ Raffinate
In Chapter 2 of this thesis the effect of extra-column dead volume in small scale SMB units is studied. It is shown that whenever the extra-column dead volume is no longer negligible compared to the column volume it has to be taken into account in the design of SMB separations to guarantee satisfying product specifications. This thesis presents guidelines and rules to calculate the extra-column dead volume for the different sections of an SMB unit and it is demonstrated how to account for it in the calculation of the SMB operating parameters. The newly developed guidelines for the calculation of the extra-column dead volume were tested and validated through detailed simulations and experiments. For the experiments a racemic mixture of (±)-3,5-bis[1-(4-methoxyphenyl)-1-methyl]hepta-3,4-diene-1,6-diyne was separated, also referred to as Allene, on CHIRALPAK™ AD using a mixture of 90/10 volume % of n-hexane and 2-propanol as mobile phase.

Further this thesis presents the design and development of an automated on-line HPLC monitoring system, and its experimental implementation on our laboratory SMB unit. The monitoring was designed to determine the average concentrations of both product streams over one process cycle, required as
feedback information for the 'cycle to cycle' controller. The results presented demonstrate that the newly developed automated on-line HPLC monitoring system allows to obtain very accurate and precise concentration measurements and overcomes the problems and uncertainties reported for systems based on the use of polarimeters (Amanullah et al., 2007; Araujo et al., 2008). This is a substantial improvement compared to the old system, since the performance of the controller is greatly affected by the quality of the feedback information from the plant.

The integrated system consisting of the SMB unit, the 'cycle to cycle' controller, and the new HPLC monitoring system was first tested for the separation of Guaifenesin enantiomers at low feed concentration using CHIRALCEL™ OD as stationary phase and ethanol as mobile phase. The results substantiate that the 'cycle to cycle' controller in spite of uncertainties in the model parameters (plant/model mismatch) is able to fulfill the product specifications and successfully rejects disturbances such as feed pump or recycle pump malfunctioning. To demonstrate the robustness of our control approach with respect to the final operating point achieved in the \((m_2, m_3)\) plane, the plant was started up at different initial operating conditions. The controller not only achieved the minimum purity specifications for all the runs but also drove the operation to almost the same final operating point in the \((m_2, m_3)\) plane.

For the first time the 'cycle to cycle' optimizing controller was experimentally implemented for a high purity chiral SMB separation of Guaifenesin enantiomers under nonlinear chromatographic conditions, i.e. at high feed concentrations up to 18.0 g/L. This is an important achievement since it is well known that the productivity of an SMB unit increases with the total feed concentration and therefore, this regime is the most interesting one for industry. The experimental runs were designed to challenge the performance of the controller and the experimental results have clearly validated the most valuable asset of the 'cycle to cycle' controller developed in the last years: the controller can deliver the specified purities and improve the productivity with the knowl-
edge of the linear adsorption behavior only, even if the separation at stake is
governed by an unknown nonlinear adsorption isotherm. This is an important
achievement since the time consuming task of determining the complete ad-
sorption isotherm for a new separation is in conflict with the industry’s need to
realize a short time to market. The controller and the approach presented in
this thesis offer a fast and reliable way to set up new chiral SMB separations.
To demonstrate this important feature of our ‘cycle to cycle’ control concept
the separation of a new compound was carried out, namely the separation
of Troeger’s Base enantiomers on the stationary phase CHIRALPAK™ AD
using pure ethanol as mobile phase. It was shown that the proposed control
concept together with the newly developed HPLC monitoring system is simple
enough to be implemented quickly and reliably for a new separation campaign.

The increasing use of SMB technology in industry, in particular for chiral
separations, has led to the development of modified SMB schemes that al-
low to increase the separation performance yet fulfilling the specified purity
specifications. One of these modifications is presented in this thesis, the in-
termittent simulated moving bed (I-SMB) process. This modification is based
on intermittent feed and product withdrawal and was first patented and com-
mercialized by the Nippon Rensui company under the name improved SMB
(ISMB) process. This thesis presents the principle of the I-SMB process, the
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tal implementation for the separation of the chiral compound (RS,RS)-2-(2,4-
difluorophenyl)butane-1,2,3-triol, an important intermediate in the production
of different antifungal drugs.

8.1 Outlook

In a classical SMB unit a feed mixture is typically separated into two prod-
cuct fractions as it is the case for chiral separations. However, in some cases
racemic mixtures of enantiomers contain an impurity which might be a by
product from the reaction or an unconverted reactant. To address the pres-
ence of impurities in the feed mixture there has been effort to develop new multi-column process schemes to realize three fraction separations within one process step. In principle two different strategies can be distinguished, namely multi-zone SMB units where two or more SMB steps are carried out either in sequence or within one SMB unit or new multi-column process schemes for three fraction separations applying the concept of intermittent feed and product withdrawal steps. A process developed in our group and belonging to the former category is the so called three-fraction separation SMB (3F-SMB), which allows to achieve ternary separations by adding an additional zone to the classical four zone SMB (Abel et al., 2004a; Paredes et al., 2004). A first modification for the latter category of processes was presented in this thesis, the intermittent simulated moving bed (I-SMB) process which not yet achieves ternary separations (Tanimura et al., 1995; Katsuo and Mazzotti, 2009).

More recently Wankat and his coworker have introduced a semicontinuous two-zone SMB/chromatography hybrid system for ternary separations (Hur and Wankat, 2005, 2006). In the year 2005, researchers at ETH Zurich have invented and patented the so-called multi-column solvent gradient purification (MCSGP) process a continuous chromatographic process that allows the use of solvent gradients and was specifically designed for three fraction separation of proteins and peptides (Aumann and Morbidelli, 2005, 2007; Aumann et al., 2007; Aumann and Morbidelli, 2008). The MCSGP process exploits the same principles as SMB, i.e. to simulate a countercurrent flow of a solid and a fluid phase by periodically switching the inlet and outlet ports of fixed-bed columns.

The development of continuous multi-column chromatographic processes for three-fraction separations of chiral compounds is a very interesting and challenging problem from an academic point of view and attracts a lot of interest from the pharmaceutical industry. Within my PhD I have been part of an important EU project ”Intenant”, a collaboration between different universities and companies across Europe. Among other things, the development of new processes for three-fraction separations is one of the goals of this project. Within our group we follow the approach of intermittent feed and product
8.1 Outlook

withdrawal strategy to realize three-fraction separations. We have developed new multi-column process schemes, comprising 2 to 4 columns, and for illustration purposes, without going into the details of the process, one of these schemes is shown in Fig. 8.1. This process comprises three columns and the switch time, $t^*$, is divided into two sub-intervals indicated as step I and step II. In step I the Feed (F) is introduced to the unit while component A, B, and C are collected. In step II all inlet and outlet ports are closed and the fluid is just circulated to move the concentration profiles along the column train similar to step II of the I-SMB process. Applying the same thinking as presented in Chapters 2 and 7 one can obtain the constraints of complete separation for linear chromatographic conditions.

The next step in this project will be to implement the proposed new multi-column process schemes experimentally on our ÄKTA$^{\text{TM}}$ explorer 100 system (GE Healthcare); first for linear chromatographic conditions and then increasing the complexity for nonlinear conditions. For the transition from linear to nonlinear conditions the application of detailed process models will be of great importance to understand the process behavior, to recognize trends, and to develop criteria that can help to decide which process scheme yields the best results in terms of separation performance for a given separation problem.
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