Enhancing the Potential of Intermittent Simulated Moving Bed Chromatography for Chiral Separations

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Abstract

Simulated Moving Bed (SMB) Chromatography is a well-established separation process which is currently applied at any scale in the chemical, pharmaceutical and biotechnological industry. The classical SMB process performs a binary split in a continuous mode of operation which makes it particularly useful for separating binary mixtures, especially isomers and enantiomers.

SMB was originally invented in the oil industry in 1961 and has been transferred to other fields of applications such as separation of sugars or enantiomers. The latter is particularly challenging since it requires on the one hand costly chiral stationary phase, which triggered the emergences of many modified mode of operations featuring higher productivities, i.e. a larger throughput per unit time and unit volume of stationary phase. On the other hand, chiral separations frequently involves more than two compounds due to the presence of either several stereocenters or of impurities stemming from upstream processes. Hence, there is a need for chromatographic processes capable of performing three-fraction separation.

This thesis addresses both research interests by proposing three new process concepts that are based on the intermittent SMB (I-SMB) process, which is itself a modification of classical SMB and was commercialized by Nippon Rensui Corporation. Although, I-SMB was shown to substantially outperform conventional SMB in terms of productivity, roughly a quarter of the adsorbent in I-SMB is not actively used in separating the feed mixture. This opens the way for two possible pathways of optimization; namely (i) enhancing the productivity of the binary separation by removing the inactive fraction of the adsorbent, and (ii) making use of the surplus adsorbent to accommodate an additional separation zone so as to extend the field of possible applications by enabling three-fraction I-SMB separations.

Following the first pathway, a new three-column intermittent SMB (3C-ISMB) process is developed which combines the classical functions of section I and IV, i.e. regeneration of solid and fluid phase, within a single section. As a result, the stationary phase is more efficiently used, which results in substantial improvements in terms of productivity without compromising purity. These improvements are convincingly demonstrated through both a comprehensive simulation study and a direct experimental comparison of 3C-ISMB and I-SMB studying the separation of Troger’s Base in ethanol on Chiralpak AD™. Furthermore, it is demonstrated how 3C-ISMB can be designed through application of Triangle Theory, which is an important advantage compared to other modified SMB processes requiring numerical optimization strategies.

Furthermore, this thesis explores the second optimization pathway thus showing how the four-section I-SMB concept can be extended to three-fraction separations by withdrawing an additional product stream during the previously non-productive substep 2. In general, it is possible to recover either the strongest or the weakest retained component of a ternary mixture during substep 2. Both options are explored and the resulting process schemes are accordingly termed 3S-ISMB and 3W-ISMB, respectively. A design methodology for
both processes based on Triangle Theory is developed and experimentally validated for 3W-ISMB by studying the separation of a mixture of the enantiomers of \(\gamma\)-Phenyl-\(\gamma\)-butyrolactone and the \((-\rangle\)-Tröger’s Base enantiomer in pure ethanol on Chiralpak AD\textsuperscript{TM}. Finally, an alternative option for three-fraction separation, namely a 3C-ISMB cascade, is presented and experimentally validated. The cascade consists of two stages each performing a binary separation by means of the 3C-ISMB technology. Thus the first stage produces an intermediate product consisting of the intermediately retained target component and either heavy or light impurities. The intermediate product is then reprocessed in a second stage so as to recover the pure target component. In the experimental part an intermediately retained stereoisomer of Nadolol is isolated from an equimolar mixture of its four stereoisomers.
Zusammenfassung


Die erste Variante der Prozessoptimierung ermöglicht die Entwicklung eines neuen Dreisäulen I-SMB (3C-ISMB) Prozesses, in welchem die klassischen Funktionen von Zone I und IV, sprich Regeneration von fester und flüssiger Phase, in einer einzigen Zone kombiniert wird. Dadurch wird die stationäre Phase effizienter ausgenutzt, was substantielle Verbesserungen bezüglich Produktivität bei gleichbleibender Produktreinheit erlaubt. Diese Verbesserungen werden durch umfangreiche Simulationsstudien dargelegt und experimentell validiert. Der experimentelle Teil untersucht die Trennung rasemischer Trögerbase in Ethanol auf Chiralpak AD und zeigt, dass die Trennleistung von 3C-ISMB auch im experimentellen Vergleich jener von I-SMB deutlich überlegen ist. Ausserdem wird gezeigt, dass 3C-ISMB mittels Dreieckstheorie einfach ausgelegt werden kann, was ein wichtiger Vorteil gegenüber anderen modifizierten SMB Prozessen ist.

Weiter untersucht diese Dissertation die zweite Möglichkeit der Prozessoptimierung und zeigt wie das Vier-Zonen I-SMB Konzept auf Dreifraktionen Trennungen ausgeweitet werden kann. Hierzu wird im ursprünglich unproduktiven zweiten Teilschritt ein zusätzlicher

Table of Contents

Acknowledgment i

Abstract iii

Zusammenfassung v

Table of Contents vii

1 Introduction 1

1.1 Chromatographic Separation of Enantiomers 2

1.2 Advanced SMB Processes 5

1.3 Intermittent Simulated Moving Bed (I-SMB) 7

1.4 Chromatographic Three-Fraction Separation 8

1.5 Objectives and Structure of this Thesis 9

2 Three fraction separation by 3W-ISMB and 3S-ISMB 11

2.1 Introduction 11

2.2 Theory and process schemes 12

2.2.1 3S-ISMB 13
2.2.2 3W-ISMB ................................................................. 19
2.2.3 Extra-column dead volume in the 3W-ISMB unit .............. 22
2.3 Experimental .......................................................... 23
  2.3.1 Experimental set-up .............................................. 23
  2.3.2 Materials .......................................................... 26
  2.3.3 Linear adsorption ............................................... 27
  2.3.4 Operating point ................................................. 27
2.4 Results and discussion ............................................. 29
2.5 Conclusion ........................................................... 32
2.6 Nomenclature ......................................................... 34

3 3C-ISMB: Description & comparative assessment ................. 37
  3.1 Introduction ......................................................... 37
  3.2 Background .......................................................... 39
    3.2.1 The conventional I-SMB process .............................. 39
    3.2.2 Short-cut design method (Triangle Theory) ............... 41
    3.2.3 Separation performance metrics ............................... 43
    3.2.4 Modeling intermittent SMB processes ....................... 43
  3.3 The 3-column I-SMB process (3C-ISMB) .......................... 45
    3.3.1 Process description and comparison to I-SMB ............ 47
    3.3.2 Process Design ................................................. 49
    3.3.3 Effect on separation performance ........................... 50
  3.4 Analysis of the cyclic steady state behavior .................... 51
    3.4.1 Exploring the \((m_{III}, m_{III})\)plane ...................... 52
    3.4.2 Exploring the \((m_{I}, m_{IV})\)plane ........................ 57
    3.4.3 Exploring highly non-linear conditions .................... 60
7.4.3 The Zorbax Extend-C18 stationary phase ...................................... 162
7.5 Conclusions ....................................................................................... 163
7.6 Nomenclature .................................................................................... 163

A Supplementary Material for Chapter 2 ............................................... 165
A.1 Extra-column dead volume in the 3W-ISMB unit .............................. 165
A.1.1 Strict Constraints .......................................................................... 165
A.1.2 Effective flow rate ratios ................................................................. 167
A.2 Nomenclature .................................................................................... 167

List of Abbreviations .............................................................................. 169
List of Figures ........................................................................................ 171
List of Tables .......................................................................................... 185
Bibliography ............................................................................................. 187
Curriculum Vitae ....................................................................................... 195
Chirality refers to nonidentity of an object with its mirror image \( [1] \), i.e. the two objects are not superimposable such as for example human hands. In chemistry, two chiral molecules, that are nonsuperimposable mirror images of each other, are called enantiomers or stereoisomers \([2]\). Chirality is due to the lack of inverse symmetry elements caused by the presence of a chiral center, a plane, or an improper axis of symmetry \([1]\). The most common reason for chirality is the presence of a tetrahedral carbon atom bound to four different chemical groups, i.e. the carbon atom represents the chiral center. Most physicochemical properties of enantiomers are identical, they only differ in the direction in which they rotate polarized light and in their interaction with other chiral substances. For the former difference enantiomers are often referred to as optically active whereas the latter has a tremendous impact for several industries, especially the pharmaceutical, agrochemical, food, and biotechnology industries. This impact stems from the fact that life is essentially constructed from L-amino acids as enantiopure building blocks \([2]\). As a result, biological receptors are chiral and interact differently with other chiral substances such as drug substances, flavours, or agrochemicals. More specifically, one enantiomer, the so-called eutomer, interacts with a biological system in the desired way, e.g. it has a therapeutic effect in the human body or acts as a pesticide, whereas the other enantiomer, the so-called distomer, might show a considerably different bioactivity. Famous examples thereof are Thalidomide where one enantiomer acts as mild sedative drug whereas the other causes teratogenic deformities in foetuses \([3]\), or Carvone where the two enantiomers have a characteristic odor of caraway and spearmint, respectively \([4]\).

Traditionally, chiral drug substances were marketed as racemates, i.e. equimolar mixture of the two enantiomers, which had tragic and fatal consequences in the case of Thalidomide. Despite the fact that the Thalidomide case spurred regulations on chiral drug substances \([5]\), nearly 90% of the chiral drugs currently in use are still administered in
CHAPTER 1. INTRODUCTION

racemic form [6]. Although regulators nowadays require to proof that the distomer is not toxic before approving racemic drugs or agrochemicals, the application thereof increases the burden for the metabolism or the environment [7]. The latter is particularly problematic in cases where the eudismic ratio, i.e. ratio of the activity of eutomer and distomer [7], is large since the metabolism or the environment is burdened for each amount of active compound with the same amount of inactive compound that does, however, not contribute to the therapeutic effect. Typical consequences of the presence of the distomer are therefore (i) increase in side-effects due to the larger dose, (ii) reduced activity due to competitive antagonistic effects of eutomer and distomer, and (iii) increased activity due to metabolic inversion of the distomer, e.g. the inactive L-isomer of Ibuprofen is metabolically converted to a large extent into the active D-form [7]. Given these consequences and given that more than half of the drugs currently on the market are chiral [6], the provision of pure single enantiomers is of increasing importance [2].

The production of pure single enantiomers is, however, challenging for the fact that most of their physicochemical properties are identical. Two different approaches, namely asymmetric synthesis and non-selective synthesis followed by resolution of the racemate, have emerged to address this issue [2]. This thesis deals with the second pathway to pure single enantiomers, more specifically with the chromatographic resolution of racemates by simulated moving bed (SMB) chromatography [8, 9]. Alternative resolution techniques are (i) kinetic and dynamic kinetic resolution, (ii) selective liquid-liquid extraction, (iii) membrane separation, (iv) diastereomeric salt resolution, and (v) crystallization. The remaining discussion in this section is restricted to chromatographic techniques, for the alternative resolution processes the reader is referred to a recent review by Lorenz and Seidel-Morgenstern [2].

1.1 Chromatographic Separation of Enantiomers

Chromatography is a well established separation technique, being defined as a process separating the components of a mixture on the basis of their differential rate of migration along a packed column percolated by a fluid phase [10]. The emergence of commercially available, stable and versatile chiral stationary phases (CSPs) made chromatography not only the most important tool for determining optical purity, but also a powerful alternative for producing pure single enantiomers on a preparative scale [11]. The versatility of the most prominent CSPs is reflected by the fact that a review of about 1'000 racemic mixtures demonstrated that about 90% of them can be separated by only four CSPs, namely Chiralcel OD, Chiralcel OJ, Chiralpak AD, and Chiralpak AS which are all manufactured by Daicel Chemical Industries [11, 12]. Besides their versatility, chromatographic separation methods are promising from an engineering point of view, since high product purity and high recovery are achievable. Moreover, they consume usually less energy than other unit operations, such as distillation, and are suitable for separation of heat sensitive components [13]. The latter feature is key to the application of chromatography in the areas of pharmaceuticals, fine chemicals, biotechnology, natural products and agrochemicals.
CHAPTER 1. INTRODUCTION

However, traditional batch chromatography has some major drawbacks concerning large-scale industrial application, namely (i) the often inefficient usage of the stationary phase, (ii) the large volumes of solvent needed, (iii) the limited purity obtained for components with small adsorptivity differences, and (iv) the discontinuity of the process [13]. In order to overcome these limitations of batch chromatography, a number of continuous chromatographic methods both cross-current, such as the rotating annular chromatograph [14], and counter-current schemes, such as the SMB process [8, 9], were proposed. The former is able to separate multiple component mixtures but its performance is the same as that of batch chromatography. The latter is a multi-column continuous binary separation process as shown in figure 1.1. It is in fact the practical implementation of the hypothetical continuous counter-current adsorber, also referred to as true moving bed (TMB) process illustrated in figure 1.2. Counter-current processes have the best possible mass transfer characteristics and thus high-purity products, even in cases of low resolution,
can be obtained. Therefore, SMB chromatography allows usually for higher productivity and lower solvent consumption as compared to batch chromatography [15, 16].

Commonly, an SMB unit consists of 6 or more columns that are divided into four sections by two inlet (desorbent/feed) and two outlet (extract/raffinate) streams. Each section has therefore a different flow rate and is characterized by a dedicated role; namely regeneration of the adsorbent (section I), desorption of the less retained component B (section II), adsorption of the more retained component A (section III) and regeneration of the desorbent (section IV) [5]. Synchronized shifting of the position of the inlet and outlet streams by one column length in direction of the fluid flow simulates a counter-current movement of the stationary phase. Due to the intrinsic port shifting discontinuity the SMB process attains a cyclic steady state whereas a proper steady state is attained in TMB. Moreover, the port shifting discontinuity makes SMB more prone to dispersion as compared to the equivalent TMB process, which can be countered by dividing one section into several columns allowing for shorter switching periods and thus a better approximation of the idealized TMB. Therefore, the very first SMB process for para-xylene recovery [8] employed 12 columns and modern para-xylene separation units employ up to 24 columns [17]. These large numbers of columns in petrochemical applications are required since the stationary phases used have typically a relatively low column efficiency, which requires a better approximation of the TMB process.

The restriction to binary separation leads to a limited area of application of the SMB technology, most frequently to the separation of isomers. The SMB technology was indeed invented in the early 1960s for that purpose, more specifically for the separation of -xylene from other C8 aromatics or n-paraffins from iso-paraffins [8, 9]. Furthermore, the SMB process has also been used for decades on a megaton scale in the sugar industry for separating fructose from glucose [18], i.e. the process was only applied by bulk chemicals manufacturers for the separation of isomers. However, with the emergence of reliable CSPs, SMB was brought to the attention of drug manufacturers as a potential technique to supplement their chiral toolbox. Thus an increased research activity on SMB began in the mid 1990s which is clearly reflected in a significant increase in yearly awarded patents [10] and publications [5] related to SMB. A detailed outline of the key developments in SMB technology can be found in table 1 of ref. [5].

Meanwhile, the SMB technology is also firmly established in non-traditional fields of ap-
Applications for chiral separations; for instance several chiral APIs are currently produced on a multiton scale using SMB chromatography [19, 20]. However, the requirements in the non-traditional fine chemical fields are considerably different from those in the traditional fields of petrochemicals and sugar separation. Probably the most important difference resides in the costs associated with the stationary phase material; in traditional petrochemical and sugar applications, large plants dedicated to a specific separation problem are used which usually employ relatively cheap stationary phase materials, such as zeolites or ion exchange resins. Chiral separations in contrast, require costly CSPs and the plants are often employed on a multi-product basis, i.e. relatively short production campaigns for one and the same product are run resulting in frequent repacking of the chromatographic columns which causes higher losses of the adsorbent and thus additional costs [21]. As a consequence, the number of columns, respectively the amount of stationary phase, should be reduced to the minimum, which is facilitated on the one hand through higher column efficiencies and on the other hand through advanced modes of operation [5]. The former allows for running a standard SMB process for chiral separations with as little as six columns, i.e. in 1-2-2-1 configuration, without compromising product purity [22]. A further reduction of the amount of stationary phase needed, i.e. a more efficient use thereof, is possible by adapting the operating conditions as discussed in the next section.

1.2 Advanced SMB Processes

The most successful alternative approaches dealing with increasing the productivity, i.e. the throughput per unit time and unit volume of stationary phase, can be subsumed as SMB processes with non-constant operating conditions. These processes are characterized by division of the switching time into two or more substeps which allows variation of the operating parameters in a stepwise manner and thus increases the number of degrees of freedom. In general, the additional complexity hampers the design as simple shortcut design methods such as Triangle Theory [23] are no longer applicable, the increased complexity is, however, compensated by a possible increase in productivity. The most prominent examples of this class of operating modes are among others VariCol (variation of the column configuration) [24], PowerFeed (variation of the internal and external flow rates) [25, 26], partial feed/partial withdrawal (variation of feed and raffinate flow rates so as to keep $Q_I$, $Q_{II}$ and $Q_{IV}$ constant) [27], ModiCon (variation of the feed concentration to influence the migration velocities) [28], and intermittent SMB (I-SMB) [29, 30], which can be regarded as special case of PowerFeed and is discussed in more detail in section 1.3.

Another straightforward method to reduce the number of columns is the adaptation of a three-section concept, i.e. the removal of the fourth section [31]. In the classical embodiment of the three-section SMB process the flow regime in sections I to III is identical to the equivalent four-section process, however, as a result of the removal of section IV no solvent is regenerated and recycled to section I. As a consequence the solvent consumption
increases and the raffinate product gets more diluted, thus this type of operation is only considered when cheap solvents such as distilled water can be used. Zang et al. proposed the combination of partial feed/partial withdrawal with the three-section concept in order to reduce the solvent consumption [32]; namely the fact that the raffinate outlet consists essentially of pure solvent at the beginning of the switch period was exploited by recycling the corresponding part of the raffinate stream to section I.

A very similar process was developed by Lee et al. [33, 34] who proposed a three-section SMB that is continuously operated, in the sense that the feed is continuously supplied and the extract continuously withdrawn. Moreover, the internal flow rates in all three sections are kept constant. For the raffinate stream, however, Lee et al. proposed two different partial recycling concepts being termed front-portion recycle and rear-portion recycle.

The former makes use of the same principle as the method proposed by Zang et al. and recycles the part of the raffinate stream that consists essentially of pure solvent. The rear-portion recycle concept illustrated in figure 1.3 is, however, fundamentally different from all the other concepts discussed so far, as it recycles the portion of the raffinate stream that is rich in the weakly retained component B to section I. Recalling the purpose of section I, i.e. regeneration of the solid phase by applying high flow rates so as to desorb the strongly retained component A, such a recycling scheme does intuitively contradict the common principles being applied in classical and modified SMB schemes. However, since the second substep, i.e. the step where B rich solution is recycled to section I, is significantly shorter than the first substep, section I is already regenerated to a large extent when the front of B starts entering section I, i.e. the front of B has a large clearing from the tail of A. To the best of the author’s knowledge such an uncommon recycling regime is quite unique and he is not aware of any other processes making use of the same principle. It is also worth pointing out, that the partial rear-portion raffinate recycle concept has not attracted the attention of the broader scientific community and has never been studied experimentally.

It has therefore yet to be proven that the claimed purity levels close to complete separation are really achievable in 1-1-1 configuration under realistic experimental conditions. This
process applying a continuous feeding strategy is likely to suffer from the influence of the port shift discontinuity and thus probably requires more than one column per section in order to obtain the claimed high purity products. Nonetheless, the idea of partial rear-portion raffinate recycle is worthwhile pursuing further and will be incorporated into I-SMB throughout this work so as to exploit the benefits of both three-section SMB with partial recycle and I-SMB, which is briefly described next.

1.3 Intermittent Simulated Moving Bed (I-SMB)

The conventional I-SMB process \[29, 30, 35\] was commercialized by Nippon Rensui Corporation and is a modification to classical SMB chromatography that was shown to significantly outperform SMB in terms of productivity \[22, 36\]. The I-SMB process is characterized by (i) a division of the switching period into two substeps, and (ii) the employment of four sections, each consisting of only one chromatographic column. In substep 1 the feed and the mobile phase (desorbent) are introduced between sections II and III and into section I, respectively, whereas the extract (containing the strongly retained component A) is withdrawn between sections I and II and the raffinate (containing the weakly retained component B) is collected from section III. Noteworthy, section IV is not used during substep 1, i.e. the volumetric raffinate flow rate equals the internal volumetric flow rate of section III. In substep 2 all inlet and outlet ports are closed, section IV is reconnected to the column train in order to adsorb the weakly retained component, and the fluid is circulated at constant flow rate through the column train so as to adjust the relative position of the concentration fronts. It is worth mentioning that the introduction of average volumetric section flow rates allows demonstrating the equivalence of I-SMB and classical SMB \[30\]. Therefore, the same design methods (Triangle Theory) \[23\] are applicable and each section of the I-SMB fulfills the same role as the corresponding section in an equivalent SMB unit, particularly the mobile and the stationary phase are regenerated in section IV and I, respectively.

Although I-SMB was previously shown to significantly outperform standard SMB \[22, 36\], a careful analysis thereof has revealed that roughly a quarter of the adsorbent used in an I-SMB unit is actually not active in separating the feed mixture. More specifically, section IV is completely idle for a relatively large fraction of the switching period, and section I is almost completely regenerated at the end of substep 1. This opens the way for two possible optimization strategies: (i) making use of the surplus adsorbent to accommodate an additional separation zone so as to extend the field of possible applications by enabling three fraction I-SMB separations, and (ii) enhancing the productivity of binary separations by removing the inactive fraction of the adsorbent in such a way that the product purities are not compromised. Both pathways will be explored throughout this thesis; the former will be the subject of chapter 2 whereas the latter can be realized by incorporating the concept of rear-portion raffinate recycle and thus reducing the number of columns to three as discussed in chapters 3 and 4.

The successful realization of the second objective will enhance the potential of intermittent
CHAPTER 1. INTRODUCTION

SMB for binary chiral separation since it reduces not only the equipment costs, but also the required effort for column repacking when switching production campaigns. The benefit of enabling three-fraction separation is discussed next.

1.4 Chromatographic Three-Fraction Separation

The separation of enantiomers frequently involves more than two compounds due to the presence of either several stereocenters or of impurities stemming from upstream processes. In case the eutomer is neither the most nor the least retained component, the standard SMB process as well as the advanced concepts discussed in section 1.2 fail in producing a pure product since these processes can only perform a binary split. Therefore, there is doubtlessly a need for SMB modifications that allow for three-fraction separation so as to increase the range of applications to more challenging multi-component separations. As a consequence, continuous chromatographic three-fraction separation is an ongoing research interest addressed by several groups as briefly reviewed in the following.

The SMB based three-fraction separation processes proposed so far can be roughly classified into two groups, namely (i) continuous processes with constant operating conditions and typically a large number of columns and (ii) semi-continuous processes with more complex operating conditions and usually a smaller number of columns. Prominent examples of the first group are the SMB cascade [37, 38] or the integration thereof in a single unit yielding an eight- or nine-zone SMB process [39, 40, 41, 42]. The 3F-SMB process [43] also belongs to this group, but is quite different since it uses only five zones and the most retained component is just trapped in a column before it is eventually eluted from the port of the loop called 0th zone. Therefore, it is restricted to systems with high selectivities between the intermediate and the most retained component. The feasibility range can, however, be extended by using an alternate opening and closing of the product ports [44]. This latter approach is considered a bridging case between the two groups of ternary separation processes. Important examples of the second group are the 2-zone SMB/chromatography hybrid system [45], the JO or pseudo-SMB process [46, 47], and the multi-column countercurrent solvent gradient purification (MCSGP) process [48, 49]. It is worth mentioning that the extension of I-SMB discussed in chapter 2 and yielding the so-called 3S-ISMB and 3W-ISMB processes [50] belongs to this second group of three-fraction SMB-like processes.

The SMB cascade has some practical advantages over the other process schemes since it is not only easy to design but also allows for (i) distributing the pressure drop over two stages, (ii) using different column sizes and switching times in the two stages, and (iii) full decoupling of the two stages using a buffer tank. The main disadvantages of the SMB cascade is the requirement for a large number of columns, typically at least twelve, which can be overcome by replacing the individual SMB stages by an advanced SMB process such as the 3C-ISMB process that is the subject of chapters 3 and 4 of this thesis. Therefore, chapter 5 will explore the promising 3C-ISMB cascade for isolating an
intermediately retained stereoisomer from a quaternary mixture.

1.5 Objectives and Structure of this Thesis

The main objective of this thesis is to enhance the potential of the I-SMB technology for chiral separations by developing closely related process concepts that exploit the stationary phase in a more efficient manner. The most important limitation of the SMB technology regarding preparative separations of chiral substances is probably its intrinsic restriction to binary separations. Therefore, this thesis has a clear focus on developing and experimentally validating three-fraction processes that can potentially extend the range of application not only to ternary mixtures, but in principle also to multi-component mixtures. Since a sheer infinite number of possible column configurations could be thought of, this work shall be restricted to configurations that can be carried out with four or less pumps. This restriction guarantees not only that a process option is implementable on the experimental equipment available at the Separation Processes Laboratory (SPL), but is also beneficial regarding retrofits of currently installed industrial SMB plants. Therefore, chapter 2 deals with the development of two process schemes aiming at facilitating three-fraction separations within a single unit. This objective can be achieved by following the first optimization pathway outlined in section 1.3, i.e. by using the conventional four sections of an I-SMB unit and employing the surplus adsorbent more efficiently by adding an additional outlet stream. More specifically, the additional outlet stream is collected during the previously non-productive substep 2 and depending on whether the weakest or the strongest retained component is collected during substep 2, the two processes are termed 3W-ISMB and 3S-ISMB, respectively. Both processes are analyzed within the frame of equilibrium theory and a modified version of Triangle Theory for the design of both processes is presented. Finally, one of the process scheme, namely the 3W-ISMB process, is studied experimentally for separating a ternary system consisting of a mixture of the enantiomers of $\gamma$-Phenyl-$\gamma$-butyrolactone and the (-)-Tröger’s Base enantiomer (artificially added as an impurity) in pure ethanol on Chiralpak AD$^\text{TM}$. Next, a step back is taken aiming first at improving the productivity of binary intermittent SMB chromatography, which eventually provides the building blocks for an efficient ternary separation by cascade operation. The first objective is addressed by following the second optimization pathway, i.e. the removal of the surplus adsorbent. Therefore, chapters 3 and 4 are dedicated to the development and experimental implementation of a novel three-column intermittent simulated moving bed (3C-ISMB) process. Finally, chapter 5 deals with the design and implementation of a 3C-ISMB cascade for three-fraction separation. In chapter 3 the new 3C-ISMB process is theoretically introduced and the applicability of a modified version of Triangle Theory for 3C-ISMB is demonstrated. Furthermore, its performance is comparatively assessed against conventional I-SMB through a thorough simulation study. The potential benefits of the new operating mode with respect to productivity is experimentally validated in chapter 4 studying the separation of racemic
Tröger’s Base in pure ethanol on Chiralpak AD™.

Finally, chapter 5 closes the bracket by demonstrating a different approach to solve three-fraction separation problems, namely the employment of a 3C-ISMB cascade. A holistic design methodology for separating multi-component mixtures from solvent and stationary phase screening to the implementation of the 3C-ISMB cascade is proposed and experimentally validated by studying the purification of an intermediately retained stereoisomer of Nadolol in Heptane/Ethanol/DEA on Chiralpak AD™.

The individual chapters of this thesis are written in a manner that they can stand alone and can be read independently. Therefore, each chapter contains all the necessary details and has consequently an introduction and a conclusion section. Nonetheless, the main body of this work is closed in chapter 6 with a summary containing the main conclusions of this thesis, i.e. it brings the individual chapters in perspective with each other and provides an outlook on future research.

At the end, an excursus on an unrelated topic, namely the challenges associated with the quantitative description of the delta-shock phenomenon [51, 52], is given in chapter 7. The delta-shock is a new type of non-classical composition fronts in non-linear chromatography that was first conjectured theoretically [51] and experimental evidence of its occurrence was reported by Mazzotti et al. in 2010 [52]. This final part of the present thesis was initially intended to be a small side project with the objective of confirming and quantitatively describing the experimental evidence of the delta shock. However, it turned out that the system is significantly more complex than expected and that the interpretation of the earlier results [52] needs to be revised. More specifically, the system studied previously cannot lead to the occurrence of delta shocks as claimed in ref [52], which will be demonstrated concisely in this brief excursus.

Finally, the appendix contains supplementary material to chapter 2 that was considered to be too long to be included in the main body of this work. Furthermore, a list of references and a short CV including a list of own publications is provided.
Three fraction separation by 3W-ISMB and 3S-ISMB

2.1 Introduction

Simulated moving bed (SMB) chromatography has been around for roughly fifty years now and was originally designed in the oil industry as a large-scale process for two-fraction separations [8, 9]. Later on its application scope was extended to the sugar industry [53] before being adapted in the 1990’s by the pharmaceutical industry for manufacturing chiral and biological drugs [5]. The latter development triggered increased research activities in the field and various modifications of the original SMB process have been reported [5]. Most of these new SMB-like processes are, however, still restricted to two-fraction separations thus limiting their applicability to the case of the separation of enantiomers in the presence of impurities or of the purification of biological compounds.

In the recent past a number of research groups have been addressing this issue with the aim of developing multi-column processes that allow for ternary or even quaternary separations [37, 39, 40, 41, 42, 44, 45, 46, 47, 51, 55]. These processes can be roughly classified into two groups, namely continuous process schemes with a large number of columns and semi-continuous processes characterized by a relatively small number of columns.

It is worth discussing the process schemes proposed so far in more detail. A straightforward solution to achieve ternary separation is the coupling of two standard SMB units either via the extract or the raffinate stream of the first unit; such SMB cascades were proposed by Wankat and coworkers \cite{37, 54}. A similar alternative is obtained by combining two units into one bigger unit with internal recycle, the so called integrated SMB unit consisting of eight or nine zones \cite{39, 40, 41, 42}. The 3F-SMB process proposed earlier \cite{56} uses a 5-zone SMB in which the most retained component is trapped inside the column and carried backwards with the simulated movement of the solid until it is eventually eluted by applying a stronger eluent. This process is, however, only feasible if the selectivity between the intermediate component and the most retained one is rather high. An alternative approach using a 5-zone SMB has been recently reported by Mun \cite{44} where alternate opening and closing of the product ports facilitates feasibility for a broader range of ternary systems. All of these process schemes belong to the group of continuous processes, in the sense that the feed and the products are continuously introduced into or withdrawn from the unit. Important semi-continuous alternatives are the 2-zone SMB/chromatography hybrid system \cite{45}, the JO process \cite{46, 47} and the multi-column countercurrent solvent gradient purification (MCSGP) \cite{55}. Interestingly reports about experimental studies on these three fraction SMB-like processes are rather rare in the open literature.

In this chapter the semi-continuous approach is followed and two four-column intermittent SMB schemes that are extensions of the semi-continuous I-SMB process \cite{22, 30} are presented; moreover the potential of these new process schemes is also demonstrated experimentally. In section 2.2 it is shown how I-SMB can be exploited to allow for ternary separations, which results in two novel process schemes. In addition, purity constraints for these new process schemes are developed. This is followed by an experimental study on the separation of a ternary system consisting of a mixture of the enantiomers of γ-Phenyl-γ-butyrolactone and the (-)-Tröger’s Base enantiomer (the impurity) in pure ethanol on Chiralpak AD™ (sections 2.3 and 2.4).

2.2 Theory and process schemes

In order to better understand the development of the new ternary separation processes it is worth recalling briefly the principle of I-SMB (see figure 2.1). Similarly to standard SMB, the I-SMB unit consists of four zones; however, in contrast to SMB the switch period is divided into two substeps. In substep I the unit is operated as an SMB without flow in section 4; in substep II all inlet and outlet ports are closed and the fluid is just circulated through the column train in order to adjust the relative position of the concentration profiles. It has been shown that I-SMB in 1-1-1-1 configuration doubles the productivity of 1-2-2-1 standard SMB whilst fulfilling high purity specifications \cite{22, 30}. This feature allows us to restrict the following discussion on processes in 1-1-1-1 configuration, i.e. on four-columns processes. Furthermore, it is noted that the use of the term section is avoided in the following since it is not as clearly defined for the intermittent processes as
CHAPTER 2. THREE FRACTION SEPARATION BY 3W-ISMB AND 3S-ISMB

Figure 2.1: Process scheme of closed loop intermittent simulated moving bed (I-SMB) chromatography. Feed (F) supply and withdrawal of raffinate (A) and extract (B) is conducted in substep I, whereas in substep II all inlet and outlet ports are closed. The black and grey arrows indicate the direction of the fluid and the solid flow, respectively.

compared to standard SMB. Hence, it is referred to the column positions instead of to sections.

From figure 2.1 it becomes apparent that in the case of a feed consisting of three species, A, B and C, the I-SMB process can be adapted to allow for three fraction separation by withdrawing an additional product stream in substep II. In principle one can collect either the most retained component (C) or the least retained component (A) during the second substep. The former approach will be referred to as 3S-ISMB as it is a three fraction I-SMB process characterized by withdrawal of the strongest component in substep II. Accordingly the alternative scheme is termed 3W-ISMB. Both approaches can be analyzed in the frame of equilibrium theory under linear chromatographic conditions; they are discussed separately in the following two subsections.

### 2.2.1 3S-ISMB

A schematic of the 3S-ISMB scheme is shown in figure 2.2 where the only modification with respect to the standard I-SMB is an additional outlet in substep II. The separation of the two weaker adsorbing components (A and B) is based on exactly the same principle as in I-SMB. The strongest retained component (C), in contrast, is just trapped inside the column and carried backwards with the simulated movement of the solid until it is eventually eluted from the column occupying the first position in substep II thus allowing for the regeneration of the solid phase.

In order to develop constraints for complete ternary separation, the propagation of the adsorption front and desorption tail of each component of the ternary mixture to be separated needs to be analyzed. In the frame of equilibrium theory under linear chromatographic conditions, the propagation velocity of species i in the SMB zone j, \( v_{ij} \), is given by
Figure 2.2: Process scheme of 3S-ISMB which follows directly from I-SMB and is characterized by an additional product stream, namely withdrawal of the most retained component (C) in substep II.

Figure 2.3: Physical plane for 3S-ISMB where coordinates are the time and the space coordinate along the unit’s columns. Each species propagates along straight characteristics, whose slope is given by the reciprocal of the velocity in (2.1). The blue characteristics represent species A, the red characteristics species B and the green ones species C. The dotted line divides the time axis in substep I and II.

\[
v_i^j = \frac{u_j / e^*}{1 + \nu H_i}
\]

(2.1)

where \(H_i\) is the Henry’s constant of component \(i\), \(u_j\) is the superficial velocity in section \(j\) and \(\nu\) is the phase ratio, i.e. \(\nu = (1 - e^*) / e^*\), \(e^*\) being the overall void fraction. Let us first apply equation (2.1) to species A, which is collected during substep I at the end of the third column. In order to fulfill the separation requirements, the adsorption front of A should not reach the end of the fourth column during substep II and the desorption tail of A should completely leave the second column during substep II. These considerations are represented graphically in the physical plane where coordinates are the time and the space coordinate along the unit’s columns, as shown in figure 2.3. In the figure each species corresponds to a different color and its propagation takes place along straight characteristics, whose slope is given by the reciprocal of the velocity in equation (2.1). The following constraints are obtained:
where \( L \) is the column length, \( t_*^I \) and \( t_*^II \) are the durations of substeps I and II, respectively. Noteworthy, the requirement for A leaving the third column in the raffinate stream, i.e. \( L \leq v_3^A t_*^I + v_4^A t_*^II \), is implicitly included in equation (2.2b) as \( v_3^A \geq v_2^A \).

For the sake of convenience, equations (2.2a) and (2.2b) are multiplied by the column’s cross-section area \( A \) and the term \( Au_j \) is replaced by \( Q_j \), \( Q_j \) being the volumetric flow rate as indicated in figure 2.2, thus yielding:

\[
\frac{Q_4 t_*^II}{\epsilon^* (1 + \nu H_A)} \leq V \quad (2.3a)
\]

\[
V \leq \frac{Q_2 t_*^I}{\epsilon^* (1 + \nu H_A)} + \frac{Q_4 t_*^II}{\epsilon^* (1 + \nu H_A)} \quad (2.3b)
\]

where \( V \) is the column volume. Let us introduce the following dimensionless flow rate ratios \( m_j \) and reduced Henry’s constants \( \tilde{H}_i \):

\[
m_j = \frac{t_*^j Q_j}{V \epsilon^*} \quad (2.4a)
\]

\[
\tilde{H}_i = 1 + \nu H_i \quad (2.4b)
\]

where \( t_*^j \) is the duration of the substep associated to flow rate \( j \), namely \( t_*^1 = t_*^I \) for \( j=1,2,3 \) and \( t_*^4 = t_*^II \) for \( j=0,4 \). Then equations (2.3a) and (2.3b) can be recast simply as:

\[
m_4 \leq \tilde{H}_A \quad (2.5a)
\]

\[
\tilde{H}_A \leq m_2 + m_4 \quad (2.5b)
\]

Analogous considerations for the adsorption fronts and desorption tails of the other two components yield the following full set of constraints for complete ternary separation in a 3S-ISMB unit:
These constraints are further simplified by transforming the dimensionless flow rate ratios \( m_j \) into a set of combined flow rate ratios \( \hat{m}_j \) as defined in the following equations:

\[
\begin{align*}
\hat{m}_0 &\equiv m_0 \quad (2.7a) \\
\hat{m}_1 &\equiv m_1 + m_4 \quad (2.7b) \\
\hat{m}_2 &\equiv m_2 + m_4 \quad (2.7c) \\
\hat{m}_3 &\equiv m_3 + m_4 \quad (2.7d) \\
\hat{m}_4 &\equiv m_4 \quad (2.7e)
\end{align*}
\]

It is worth noting that these combined flow rate ratios \( \hat{m}_j \) lose the physical meaning which is usually associated to the flow rate ratios \( m_j \); these definitions are in fact driven by the structure of the physical constraints given in equations (2.6a) to (2.6f). With this transformation, equations (2.6a) to (2.6f) reduce to the following simple inequalities:

\[
\begin{align*}
\hat{m}_4 &\leq \tilde{H}_A \quad (2.8a) \\
\tilde{H}_A &\leq \hat{m}_2 \quad (2.8b) \\
\hat{m}_3 &\leq \tilde{H}_B \quad (2.8c) \\
\tilde{H}_B &\leq \hat{m}_1 \quad (2.8d) \\
\hat{m}_1 + \hat{m}_2 + \hat{m}_3 - \hat{m}_4 &\leq \tilde{H}_C \quad (2.8e) \\
\tilde{H}_C &\leq \hat{m}_1 + \hat{m}_2 + \hat{m}_0 \quad (2.8f)
\end{align*}
\]

These constraints can be represented graphically in the \((\hat{m}_2, \hat{m}_3)\) plane (see figure 2.4), where equations (2.8b) and (2.8c) define a triangular region within which complete separation of A and B can be achieved. It is worth noting that equation (2.8f) can always be independently fulfilled by choosing \( \hat{m}_0 \) appropriately. Furthermore, there is always a feasible range for \( \hat{m}_4 \); hence equation (2.8a) is conveniently replaced by
CHAPTER 2. THREE FRACTION SEPARATION BY 3W-ISMB AND 3S-ISMB

Figure 2.4: Triangular region of complete separation for 3S-ISMB in the $(\hat{m}_2, \hat{m}_3)$ plane and critical line $(\hat{m}_3 \leq -\hat{m}_2 + \tilde{H}_C - H_B + \varphi \tilde{H}_A)$ below which complete ternary separation is feasible. The critical line is shown for three different values of $\tilde{H}_C$ and subfigure (c) shows that the process becomes infeasible if $\tilde{H}_C \leq (2 - \varphi)\tilde{H}_A + \tilde{H}_B$. 
where $0 \leq \varphi \leq 1$. However, the constraints on $\hat{m}_1$ defined by equations (2.8d) and (2.8e) are of a different nature. The lower bound on $\hat{m}_1$ depends on $\tilde{H}_B$ only, whereas the upper bound depends on $\tilde{H}_C$ as well as on $\hat{m}_2$, $\hat{m}_3$ and $\hat{m}_4$, which becomes clear by recasting equations (2.8d) and (2.8e) as:

$$\tilde{H}_B \leq \hat{m}_1 \leq \tilde{H}_C - \hat{m}_2 - \hat{m}_3 + \hat{m}_4$$

Therefore, a feasible range of $\hat{m}_1$ values only exists when the upper bound in equation (2.10) is larger than the lower bound, i.e. when the operating point in the $(\hat{m}_2, \hat{m}_3)$ plane is chosen below a critical straight line with negative slope given by the linear inequality

$$\hat{m}_3 \leq -\hat{m}_2 + \tilde{H}_C - \tilde{H}_B + \varphi \tilde{H}_A$$

The triangular region of complete separation together with the critical line defined by equation (2.11) is shown in figure 2.4 for three systems with different selectivities. It is noted that these plots only provide information on the feasibility of the process and on the choice of the operating point in the $(\hat{m}_2, \hat{m}_3)$ plane. For the full region of complete separation a three-dimensional plot in the space $(\hat{m}_1, \hat{m}_2, \hat{m}_3)$ for a fixed value of $\varphi$ would be required. For the sake of brevity the corresponding 3D plots are not shown, but it is noted that the three-dimensional region of complete separation becomes larger as $\varphi$ increase, which leads however to a higher solvent consumption.

At this point it is worth commenting on the feasibility of the 3S-ISMB concept depending on the selectivities of the components to be separated. From equation (2.11) and figure 2.4 it can be readily seen that the 3S-ISMB process becomes infeasible if the critical line intersects the diagonal at $(\tilde{H}_A, \tilde{H}_A)$ or below. Feasibility of the process is therefore solely determined by the y-axis intersect of the critical line, i.e. the term $\tilde{H}_C - \tilde{H}_B + \varphi \tilde{H}_A$. Furthermore it is obvious that the relative position of the critical line with respect to the triangular region shifts downwards if the selectivities between the most retained component and the other two species decrease. If these selectivities reach a value that causes the critical line to intersect the diagonal at $(\tilde{H}_A, \tilde{H}_A)$, no feasible operating points in the $(\hat{m}_2, \hat{m}_3)$ plane can exist. Therefore it is concluded that the 3S-ISMB process becomes infeasible if

$$\tilde{H}_C \leq (2 - \varphi)\tilde{H}_A + \tilde{H}_B$$

This result is in accordance with previous studies on the 5-zone 3F-SMB process mentioned above, as expected since the separation is based on very similar principles. To overcome this difficulty an alternative process has been developed and is presented in the next subsection.
CHAPTER 2. THREE FRACTION SEPARATION BY 3W-ISMB AND 3S-ISMB

2.2.2 3W-ISMB

As already mentioned above, it is also possible to collect the weakest adsorbing component during the second substep. This requires, however, more modifications to the original I-SMB process than in the 3S-ISMB case. With reference to figure 2.5, it is to be noted that contrary to I-SMB (see figure 2.1), in a 3W-ISMB process, all four columns are in use during substep I. Columns 1 and 2 are disconnected from the column train in order to elute the strong component C and the intermediate component B, respectively. The remaining columns are connected in series and fed with the mixture to be separated. After substep I, column 1 is completely regenerated and is not used in the second substep; the remaining three columns are connected in series and fed with pure eluent in order to adjust the relative position of the composition fronts and to elute component A.

The purity constraints for 3W-ISMB were derived in the same manner as for 3S-ISMB (see section 2.2.1). The propagation paths of the different species in the physical plane are illustrated in figure 2.6. The same definitions for dimensionless flow rate ratios and
reduced Henry’s constants, given in equations (2.4a) and (2.4b), apply. Therefore, another set of six inequalities can be obtained as given by:

\[
\begin{align*}
m_3 &\leq \tilde{H}_A \tag{2.13a} \\
\tilde{H}_A &\leq m_4 \tag{2.13b} \\
m_3 + m_4 &\leq \tilde{H}_B \tag{2.13c} \\
\tilde{H}_B &\leq m_2 + m_4 \tag{2.13d} \\
m_2 + m_3 + m_4 &\leq \tilde{H}_C \tag{2.13e} \\
\tilde{H}_C &\leq \begin{cases} 
  m_1 + m_2 + m_4 & (\tilde{H}_C \leq m_2 + m_3 + 2m_4) \\
  m_1 + m_2 + 2m_4 & (\tilde{H}_C > m_2 + m_3 + 2m_4) 
\end{cases} \tag{2.13f}
\end{align*}
\]

These equations are slightly more complicated than the ones for 3S-ISMB (see equations (2.6a) to (2.6f)) as two different cases have to be considered to describe the behavior of the tail of the most retained component. Also these constraints can be simplified by transforming the flow rate ratios \(m_j\) into a set of combined flow rate ratios:

\[
\begin{align*}
\hat{m}_1 &\equiv m_1 + m_2 + m_4 \tag{2.14a} \\
\hat{m}_2 &\equiv m_2 + m_4 \tag{2.14b} \\
\hat{m}_3 &\equiv m_2 + m_3 + m_4 \tag{2.14c} \\
\hat{m}_4 &\equiv m_4 \tag{2.14d}
\end{align*}
\]

Note that the combined flow rate ratios are defined differently than in the case of the 3S-ISMB process (see equations (2.7a) to (2.7e)) because of the different structure of equation (2.13c) with respect to equation (2.6e). Applying the combined flow rate ratios defined above, equations (2.13a) to (2.13f) reduce to

\[
\begin{align*}
\hat{m}_3 - \hat{m}_2 &\leq \tilde{H}_A \tag{2.15a} \\
\tilde{H}_A &\leq \hat{m}_4 \tag{2.15b} \\
\hat{m}_3 - \hat{m}_2 + \hat{m}_4 &\leq \tilde{H}_B \tag{2.15c} \\
\tilde{H}_B &\leq \hat{m}_2 \tag{2.15d} \\
\hat{m}_3 &\leq \tilde{H}_C \tag{2.15e} \\
\tilde{H}_C &\leq \begin{cases} 
  \hat{m}_1 & (\tilde{H}_C \leq \hat{m}_3 + \hat{m}_4) \\
  \hat{m}_1 + \hat{m}_4 & (\tilde{H}_C > \hat{m}_3 + \hat{m}_4) 
\end{cases} \tag{2.15f}
\end{align*}
\]

These equations can be represented graphically in the \((\hat{m}_2, \hat{m}_3)\) plane (see figure 2.7). Equations (2.15d) and (2.15e) define a right triangular region of complete separation,
Figure 2.7: Triangular region of complete separation for 3W-ISMB in the \((\tilde{m}_2, \tilde{m}_3)\) plane together with the critical line. In the case of 3W-ISMB the critical line has a positive slope which renders the process feasible for any combination of \(\tilde{H}_i\)-values. The critical line is independent of \(\tilde{H}_C\), therefore it does not intersect the triangular region below a certain selectivity between component B and C (see subfigure (b)), i.e. in these cases the region of complete separation is determined by \(\tilde{H}_B\) and \(\tilde{H}_C\) only.

whilst equations (2.15a) and (2.15c) can be combined to obtain two equations for a critical line, namely

\[
\begin{align*}
\tilde{m}_3 &\leq \tilde{m}_2 + \tilde{H}_A \\
\tilde{m}_3 &\leq \tilde{m}_2 + \tilde{H}_B - \tilde{m}_4
\end{align*}
\] (2.16a)  
(2.16b)

Similarly to 3S-ISMB \(\tilde{m}_4\) is replaced by

\[
\tilde{m}_4 = \frac{\tilde{H}_A}{\varphi}
\] (2.17)

where \(0 \leq \varphi \leq 1\), hence the equation for the critical line simplifies to

\[
\tilde{m}_3 \leq \tilde{m}_2 + \min \left( \tilde{H}_A, \tilde{H}_B - \frac{\tilde{H}_A}{\varphi} \right)
\] (2.18)

This means that the critical line, below which complete ternary separation is feasible, is parallel to the diagonal in the \((\tilde{m}_2, \tilde{m}_3)\) plane and that complete ternary separation is always feasible. However, the region of complete separation can become very narrow if the selectivity between the weak and the intermediate component is small. Finally it is noteworthy that the whole triangular region becomes accessible if
\[ \tilde{H}_C \leq \begin{cases} \tilde{H}_A + \tilde{H}_B & \left(1 + \frac{1}{\varphi}\right) \tilde{H}_A \leq \tilde{H}_B \\ \frac{2\tilde{H}_B - \tilde{H}_A}{1 + \frac{1}{\varphi}} & \left(1 + \frac{1}{\varphi}\right) \tilde{H}_A > \tilde{H}_B \end{cases} \quad (2.19) \]

as shown in figure 2.7.b.

2.2.3 Extra-column dead volume in the 3W-ISMB unit

In section 2.3 an experimental study on the 3W-ISMB process is presented which was carried out on a lab-scale 3W-ISMB unit. In lab-scale units the extra-column dead volume can be easily of the same order of magnitude as the column volume and thus being not negligible. Therefore it is necessary to revise the purity constraints developed above in order to explicitly account for the increase in residence time due to the additional dead volume. For the sake of brevity these additional constraints are only derived for 3W-ISMB as only this process is studied experimentally.

In previous publications it has been shown that the extra-column dead volume can be accounted for, both in conventional SMB [57, 58] as well as in I-SMB units [22] by using an effective flow ratio \( \bar{m}_j \) which is defined as

\[ \bar{m}_j = m_j - m^D_j = \frac{t_0^\ast Q_j}{V^\ast \epsilon} - \frac{V^D_j}{V^\ast \epsilon} \quad (2.20) \]

where \( \bar{m}_j \) is the effective flow rate ratio in section \( j \), \( V^D_j \) is the extra-column dead volume in section \( j \) and \( m^D_j \) is defined as \( m^D_j = V^D_j/(V^\ast \epsilon) \).

It has been shown that the same purity constraints defined by ”Triangle Theory” [23] apply in small-scale units when \( m_j \) is replaced by \( \bar{m}_j \) [57, 58]. However, in a 3W-ISMB unit the situation is different since the fluid in a large part of the extra-column dead volume, namely the tubing from the outlet manifold to the inlet manifold of the next column, remains stagnant when the column is disconnected from the column train. Therefore, additional constraints especially on the fronts and tails of the strongest retained component have to be imposed.

With reference to figure 2.6 it is noted that in the derivation of the 3W-ISMB constraints above where extra-column dead volume is neglected, component C is allowed to break through column 2 during substep II into column 3. However, as the tubing between outlet manifold of column 2 and inlet manifold of column 3 remains stagnant for the following two switches, any quantity of component C entering this part of the tubing would remain there until this particular tubing becomes reconnected to the column train, i.e. when the column has moved to position 3. Once this happens, any residue of component C would enter column 4 thus spoiling the purity of either the raffinate or the extract-2 stream. In order to prevent such pollution, it is necessary to impose a more stringent constraint on the front of C, so as to avoid breakthrough of component C in column 2. As a result a similar condition as in the case of 3S-ISMB is obtained, namely that C is trapped in the column and just carried backwards until it is eluted from column 1. In the case of
3S-ISMB this condition rendered complete ternary separation infeasible for low selectivity systems, the same situation can therefore occur in 3W-ISMB if the extra-column dead volume is strictly taken into account, as shown in detail in section A.1.1. For the remaining part of this chapter these stringent constraints are explicitly relaxed and component C is allowed to break through column 2. By doing so it is ensured that there is a feasible operating region for the process but one also expects some pollution from component C in extract-2 originating from the temporarily stagnant part of the tubing. Nonetheless, extra-column effects are accounted for by introducing effective flow rate ratios $m_j$, which are defined as:

$$m_1 \equiv m_1 + m_2 + m_4 - m_2^D$$  \hspace{1cm} (2.21a)
$$m_2 \equiv m_2 + m_4 - m_1^D$$  \hspace{1cm} (2.21b)
$$m_3 \equiv m_2 + m_3 + m_4 - m_2^D$$  \hspace{1cm} (2.21c)
$$m_4 \equiv m_4 - m_1^D \equiv \frac{\tilde{H}_A}{\varphi}$$  \hspace{1cm} (2.21d)

with

$$m_1^D = \frac{V_1^D}{V_\epsilon^*}$$  \hspace{1cm} (2.22a)
$$m_2^D = \frac{V_2^D}{V_\epsilon^*}$$  \hspace{1cm} (2.22b)

where $V_1^D$ represents the total extra-column dead volume between two successive column, i.e. the tubing between inlet manifold and column inlet, between column outlet and outlet manifold and from the outlet manifold to the inlet manifold of the next column; whereas $V_2^D$ includes the tubing between inlet manifold and column inlet as well as the tubing from the column outlet to the outlet manifold.

The critical line (see equation (2.18)) can be recast as:

$$\bar{m}_3 \leq \bar{m}_2 + \min \left( \tilde{H}_A + 2m_1^D - m_2^D, \tilde{H}_B - \frac{\tilde{H}_A}{\varphi} + m_1^D - m_2^D \right)$$  \hspace{1cm} (2.23)

For more details on the derivation of equations (2.21) to (2.23) the reader is referred to section A.1.2.

### 2.3 Experimental

#### 2.3.1 Experimental set-up

The experimental set-up for the 3W-ISMB process is based on a modified ÄKTA™ explorer 100 system (GE Healthcare Europe GmbH, Freiburg, Germany) [43]. The program
controlling all the devices is based on the standard UNICORN™ software (GE Healthcare Europe GmbH, Freiburg, Germany). The experiments were carried out in a 1-1-1-1 open loop configuration.

The laboratory unit was set up according to the flowsheet shown in figure 2.8. The inlet and outlet manifolds 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. Three multi-position valves are connected to the inlet manifolds and to the pumps delivering feed and solvent, respectively. Another four multi-position valves are connected to the outlet manifolds in order to collect the three product streams and the regenerated solvent stream from the outlet port. Finally two additional valves allow for switching between open and closed loop configuration (V-9) and for switching from feed solution to pure solvent (V-5) for cleaning the unit. Note that this set-up can be implemented easily on an existing SMB unit as no additional pumps are required, namely only two additional multi-position valves with the corresponding tubing are necessary to accommodate an additional inlet and outlet stream.

As discussed above in section 2.2.3 the extra-column dead volume plays a crucial role in labscale SMB units and consists of three different tubing parts. Namely from the inlet manifold to the column inlet ($V_a = 0.03$ ml), from the column outlet to the outlet manifold ($V_b = 0.02$ ml) and from the outlet manifold to the inlet manifold of the following column ($V_c = 0.18$ ml). The volumes of these tubing parts have been determined very precisely using TTBB (1,3,5-tris-tert-butylbenzene) as a tracer, the details being reported elsewhere [22, 58]. Using these values, $V_1^D$ and $V_2^D$ are equal to 0.23 ml and 0.05 ml, respectively.
Figure 2.8: Flowsheet of the experimental set-up consisting of two binary gradient pumps, four chromatographic columns equipped with an inlet and an outlet manifold and nine multiposition valves.
2.3.2 Materials

This work studies the separation of a mixture consisting of racemic $\gamma$-Phenyl-$\gamma$-butyrolactone (denoted by A and B) and the (-)-Tröger’s Base enantiomer (C) in pure ethanol separated on Chiralpak AD™ ($Q = 0.5$ ml/min, $c_{F,1} = 0.5$ g/l); P denotes the injection peak. The model system was prepared by dissolving 106.12 mg of the as-prepared (-)-Tröger’s Base (component C) and 204.25 mg $\gamma$-Phenyl-$\gamma$-butyrolactone racemate (components A and B) in 156.82 g ethanol, i.e. the concentration of all three solutes was 0.5 g/l; the chromatogram of this mixture is shown in figure 2.9.

The Chiralpak AD™ stainless steel columns (15 cm $\times$ 0.46 cm, 20 $\mu$m particle size) were prepacked by the manufacturer and were used for the separation in the 3W-ISMB unit as well as for analytical purposes. Namely, the product streams were analyzed on a Dionex Ultimate 3000 HPLC unit (Sunnyvale, CA, USA) using the same mobile phase as in the preparative application. The overall void fraction, $\epsilon^*$, of each column was determined by injecting 1,3,5-tris-tert-butylbenzene (Sigma-Aldrich Chemie GmbH, Buchs, Switzerland), which is considered to be non-retained, according to the following equation

$$\epsilon^* = \frac{t_0Q}{V}$$ (2.24)

where $V$ is the column volume, $Q$ is the applied flow rate and $t_0$ is the residence time of
2.3.3 Linear adsorption

The Henry’s constants of the three solutes, i.e. γ-Phenyl-γ-butyrolactone (species A and B) and (-)-Tröger’s Base (species C), where determined by measuring the retention time of a diluted pulse injection according to the relationship

\[ H_i = \frac{\epsilon^* t_{R,i} - t_0}{t_0} \]  \hspace{1cm} (i = A, B, C)

where \( H_i \) is the Henry’s constant of solute \( i \) and \( t_{R,i} \) is the retention time of solute \( i \) \((i=A,B,C)\). It is further noted that \( t_0 \) and \( t_{R,i} \) were corrected with the dead time of the HPLC unit. All experiments were carried out at \( T = 23\pm1^\circ C \). The system characteristics are reported in table 2.1.

Table 2.1: System characteristics

<table>
<thead>
<tr>
<th>Column</th>
<th>Linear isotherm</th>
<th>(±)-γ-Phenyl-γ-butyrolactone</th>
<th>(−)-Tröger’s Base</th>
</tr>
</thead>
<tbody>
<tr>
<td>( A [\text{cm}^2] )</td>
<td>0.166</td>
<td>1.58</td>
<td>5.41</td>
</tr>
<tr>
<td>( \epsilon^* [-] )</td>
<td>0.68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \Delta P_{\text{max}} [\text{bar}] )</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( L [\text{cm}] )</td>
<td>15</td>
<td>2.49</td>
<td>3.54</td>
</tr>
<tr>
<td>( \tilde{H}_i )</td>
<td>1.74</td>
<td>2.17</td>
<td></td>
</tr>
</tbody>
</table>

2.3.4 Operating point

Using the values given in table 2.1 and analyzing the system in the frame of the theory explained in section 2.2, it becomes clear that complete ternary separation of this model system is only feasible in a 3W-ISMB unit with negligible extra-column dead volume (see figure 2.10a) and becomes infeasible for the 3S-ISMB process (see figure 2.10b). It is further noted, that a strict consideration of extra-column effects according to section A.1.1 renders also 3W-ISMB on the labscale unit infeasible. Nevertheless the 3W-ISMB concept is implemented on the experimental set-up in order to prove the purity constraints developed above and to demonstrate the potential of this technology for large-scale applications where the extra-column dead volume would be negligible and the process would be feasible.

The operating point for 3W-ISMB in terms of \( \bar{m}_j \)-values as defined in equations (2.21a) to (2.21d) can be chosen graphically as shown in figure 2.11a. Once the operating point in the \((\bar{m}_2, \bar{m}_3)\) plane is selected, the duration of substep I and II, i.e. \( t^*_s \), needs to be determined in order to calculate the actual flow rates \( Q_j \). This can be done by solving
CHAPTER 2. THREE FRACTION SEPARATION BY 3W-ISMB AND 3S-ISMB

Figure 2.10: Graphical analysis of the model system according to 2.1. Triangle and critical line for complete separation are shown for both the 3W-ISMB process (a) and the 3S-ISMB process (b). In both cases the upper limit of $\varphi = 1$ was chosen and the extra-column dead volume was neglected. Moreover, (b) shows that 3S-ISMB is infeasible for this model system.

Figure 2.11: (a) Operating point of the four experimental runs $\alpha$ to $\delta$ represented in the $(\bar{m}_2, \bar{m}_3)$ plane. Two critical lines are shown; the one in red applies for run $\alpha$ only, whereas the black one applies for runs $\beta$ to $\delta$. The upward shift is due to a smaller value of $\bar{m}_4$. (b) Purity of the three product streams plotted against the $\bar{m}_2$-value of the operating point.
an optimization problem that aims at maximizing the feed throughput at minimal switch
time and minimal solvent consumption under the following constraints: the selected $m_j$-
values are applied and the maximum allowable pressure drop in the columns cannot be
overcome. Such an optimization problem can be formulated as follows:

\[
\begin{align*}
\text{minimize} & \quad [-\lambda_F Q_3 t_1^* + \lambda_S (Q_1 + Q_2) t_1^* + \lambda_S Q_4 t_2^* + \lambda_t (t_1^* + t_2^*)] \\
\text{subject to} & \quad \frac{L}{A} \phi Q_1 - \Delta P_{max} \leq 0 \\
& \quad \frac{L}{A} \phi Q_2 - \Delta P_{max} \leq 0 \\
& \quad \frac{L}{A} \phi Q_3 - \Delta P_{max} \leq 0 \\
& \quad \frac{L}{A} \phi Q_4 - \Delta P_{max} \leq 0 \\
& \quad \bar{m}_1 = \frac{t_1^* Q_1}{V \epsilon^*} + \frac{t_2^* Q_2}{V \epsilon^*} + \frac{t_2^* Q_3}{V \epsilon^*} + \frac{t_2^* Q_4}{V \epsilon^*} - m_2^D \\
& \quad \bar{m}_2 = \frac{t_1^* Q_2}{V \epsilon^*} + \frac{t_1^* Q_4}{V \epsilon^*} - m_1^D \\
& \quad \bar{m}_3 = \frac{t_1^* Q_2}{V \epsilon^*} + \frac{t_1^* Q_3}{V \epsilon^*} + \frac{t_2^* Q_4}{V \epsilon^*} - m_2^D \\
& \quad \bar{m}_4 = \frac{t_1^* Q_4}{V \epsilon^*} - m_1^D
\end{align*}
\] (2.26)

where $L$ and $A$ are the column length and cross-section area, respectively, $\Delta P_{max}$ is the
maximum allowable pressure drop, $\lambda_F$, $\lambda_S$ and $\lambda_t$ are weighting factors for the different
elements of the objective function. Finally, $\phi$ is the pressure drop factor according to
Darcy’s law, i.e.

\[
\phi = \frac{\Delta P_j A}{Q_j L}
\] (2.27)

For the sake of simplicity, the optimization problem (see equation (2.26)) was only solved
for the first experimental run, i.e. run $\alpha$, and the substep durations were kept constant
for the subsequent runs, i.e. runs $\beta$ to $\delta$. The substep durations were determined as $t_1^* = 1.50$ min and $t_2^* = 3.98$ min, the corresponding flow rates for the four experimental
runs are reported in table 2.2 together with the graphically selected $m_j$-values.

\subsection{2.4 Results and discussion}

The compositions and the purities of the three product streams at cyclic steady state for
the four operating points reported in table 2.2 are given in table 2.3.

The purities are defined as:
Table 2.2: Operating conditions for the experimental runs α to δ with substep durations of 1.50 min and 3.98 min for substep I and substep II

<table>
<thead>
<tr>
<th>Run</th>
<th>Flow rate (ml/min) Q₁ Q₂ Q₃ Q₄</th>
<th>Flow rate ratio μ₁ μ₂ μ₃ μ₄</th>
</tr>
</thead>
<tbody>
<tr>
<td>α</td>
<td>1.31 0.52 0.39 0.85</td>
<td>3.59 2.32 2.77 1.86</td>
</tr>
<tr>
<td>β</td>
<td>1.92 0.51 0.38 0.82</td>
<td>4.04 2.24 2.68 1.79</td>
</tr>
<tr>
<td>γ</td>
<td>2.00 0.44 0.38 0.82</td>
<td>4.05 2.18 2.62 1.79</td>
</tr>
<tr>
<td>δ</td>
<td>2.06 0.36 0.38 0.82</td>
<td>4.04 2.11 2.55 1.79</td>
</tr>
</tbody>
</table>

where i=A for the purity of the raffinate (the stream where the less retained enantiomer of γ-Phenyl-γ-butyrolactone is collected), i=B for extract-2 (the stream where the more retained enantiomer of γ-Phenyl-γ-butyrolactone is collected) and i=C for extract-1 (the stream where (-)-Tröger’s Base is collected).

Furthermore, figure 2.11 shows the position of the operating points in the (μ₃, μ₄) plane as well as the purities of all product streams as a function of μ₂. In the following the experimental performance of these runs are discussed with reference to the theoretical design criteria for 3W-ISMB presented in section 2.2.3.

With reference to figure 2.11a it is noted that the μ₄-value was decreased from run α to run β and kept constant for the following two runs, i.e. runs γ and δ. Therefore two critical lines are shown in figure 2.11a, namely the red line belonging to run α and the black line belonging to the other three runs. It is further noted that the operating point α lies above the critical line, whereas operating points β to δ lie below it.

Since the position of the operating point with respect to the critical line determines the purity of the raffinate, pollution of the raffinate from component B for run α is expected, whereas a pure raffinate should be obtained in runs β to δ. In figure 2.11b the triangles representing the raffinate purity clearly illustrate that the purity of run α is indeed significantly lower as compared to the other three runs which are close to purity. The small fluctuations of the purities in runs β to δ are attributed to the fact that the operating points lie very close to the critical line, i.e. a small shift of either the operating point due to flow rate fluctuations or the boundaries due to temperature fluctuations can cause a decrease in the raffinate purity. Nonetheless, it can be stated that the general trends as shown in figure 2.11b are in good agreement with the prediction from theory.

Provided that the lower bound for μ₄ is not violated, the purities of extract-1 and extract-2 depend on the position of the operating point with respect to the triangle only. It is noted that the vertical line of the triangle marks the boundary for the extract-1 purity, i.e. an operating point to the left of that boundary leads to pollution from component B in extract-1, whereas an operating point above the horizontal line results in a polluted extract-2.
### Table 2.3: Concentrations of all three solutes in the outlet streams and corresponding product purities for runs α to δ.

<table>
<thead>
<tr>
<th>Run</th>
<th>Raffinate - A</th>
<th></th>
<th>Extract-2 - B</th>
<th></th>
<th>Extract-1 - C</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>c_A [g/l]</td>
<td>c_B [g/l]</td>
<td>c_C [g/l]</td>
<td>P_A</td>
<td>c_A [g/l]</td>
<td>c_B [g/l]</td>
</tr>
<tr>
<td>α</td>
<td>0.0835</td>
<td>0.0084</td>
<td>0.0004</td>
<td>90.6%</td>
<td>0.0146</td>
<td>0.0308</td>
</tr>
<tr>
<td>β</td>
<td>0.0886</td>
<td>0.0002</td>
<td>0.0003</td>
<td>99.5%</td>
<td>0.0126</td>
<td>0.0500</td>
</tr>
<tr>
<td>γ</td>
<td>0.0922</td>
<td>0.0003</td>
<td>0.0003</td>
<td>99.2%</td>
<td>0.0150</td>
<td>0.0436</td>
</tr>
<tr>
<td>δ</td>
<td>0.0697</td>
<td>0.0013</td>
<td>0.0000</td>
<td>98.1%</td>
<td>0.0169</td>
<td>0.4754</td>
</tr>
</tbody>
</table>
CHAPTER 2. THREE FRACTION SEPARATION BY 3W-ISMB AND 3S-ISMB

Figure 2.11 shows that the general trends for the purities of extract-1 and extract-2 are in good agreement with theory. Namely an extract-1 purity of 99.6% for runs $\alpha$ to $\gamma$ was observed and a slightly lower purity for run $\delta$, whose corresponding operating point lies outside the triangle of complete separation.

The purity of extract-2 increases steadily from 89.2% (run $\alpha$) to 94.3% (run $\delta$), which is in agreement with theory since the operating point moves away from the horizontal boundary of the triangle. However as the operating points lie well inside the region of complete separation, a much higher purity would be expected. There are two main reasons explaining such an unexpected low purity of extract-2, namely the pollution caused by component C stemming from the temporarily stagnant part of the extra-column tubing and the axial dispersion, which is not accounted for in triangle theory. The latter needs some further discussion since the effect of dispersion is much more prominent in 3W-ISMB as compared to standard SMB.

Dispersive effects are causing more relative pollution in 3W-ISMB units because of a different internal concentration profile. Any quantity of component B entering the unit in column 3 is eluted after one switch from the same column, i.e. when it is in position 2. This requires not only baseline separation between A and B, but also results, for the feed concentrations studied, in the formation of a component B peak that has the Gaussian shape typical of column chromatography. As a consequence, the relative pollution due to dispersion is much more significant than in standard SMB where an internal concentration profile with large plateaus characteristic of countercurrent operations is built up and where it is known that axial dispersion has a minor effect.

Furthermore it is noted that dispersion causes pollution of extract-2 from both component A and component C as shown in table 2.3. As expected the decrease of $m_4$ from run $\alpha$ to run $\beta$ causes an increased pollution from component A, although the overall purity gets better because moving away from the horizontal boundary results in lower pollution from C which compensates for the larger amount of A polluting extract-2. In the following runs $\gamma$ and $\delta$, $m_4$ was kept constant, hence no change in the relative amount of A was observed. Therefore the shift downwards to the left causes a significant increase in the overall extract-2 purity as less and less C is present in extract-2.

2.5 Conclusion

In this chapter two intermittent four columns SMB processes for ternary separations have been presented. In both processes the switch time is divided into two substeps, i.e. a first substep during which the feed is introduced to the unit and second substep without feeding. The main difference between the two processes is the sequence of product withdrawal. One process is characterized by withdrawal of the most retained component during the second substep, whilst the other two product streams are collected during substep I. In the other process presented, the least retained component is collected during substep II, consequently the most retained and the intermediate retained component are withdrawn in the first substep. Due to this difference the processes were termed 3S-ISMB
and 3W-ISMB, respectively.
Both 3S-ISMB and 3W-ISMB have been analyzed in the frame of equilibrium theory. For both processes a region of complete ternary separation similar to the classical triangle theory could be derived. This analysis revealed that on the one hand 3W-ISMB always allows for complete ternary separation no matter what combinations of Henry’s constants characterize the ternary mixture to separate. 3S-ISMB on the other hand becomes infeasible if the selectivity between the intermediate and the most retained component is not large enough. Furthermore the effect of extra-column dead volume was discussed, thus demonstrating that the latter becomes very important in small-scale SMB units where the volume of the tubing between the columns is of the same order of magnitude as the column volume. For 3W-ISMB it has been shown that additional constraints are necessary when the extra-column dead volume is non-negligible and that these additional constraints may also lead to situations where complete ternary separation becomes infeasible.

After analyzing the two processes theoretically a model system for experimental validation has been presented which consisted of a mixture of the enantiomers of γ-Phenyl-γ-butyrolactone and the (-)-Tröger’s Base enantiomer in pure ethanol on the CSP Chiralpak AD™. Analysis of the model system chosen revealed that both 3S-ISMB and 3W-ISMB with non-negligible extra-column dead volume were infeasible, whereas 3W-ISMB with negligible extra-column dead volume is always feasible. Therefore 3W-ISMB was chosen for experimental validation, although its potential could only be demonstrated on a small-scale unit where complete ternary separation is not possible due to extra-column effects.

In the experimental section it has been shown that 3W-ISMB can be easily implemented on an existing SMB unit by making only a few modifications and that most importantly no additional pumps are required. Furthermore, the experimental results for this process have proven the applicability of the modified triangle theory for ternary separation. In addition the potential of the new process has been demonstrated successfully; as purities of at least 94% for all three product streams were obtained despite the fact that the small-scale unit does not allow for complete ternary separation. This is a result of both axial dispersion and non-negligible extra-column dead volume effects. In contrast to standard SMB the latter effect can not be eliminated completely due to a periodic switch between disconnected and interconnected mode. As far as axial dispersion is concerned a much more significant effect occurs in 3W-ISMB as compared to standard SMB, since the intermediate retained component (B) has an internal concentration profile with Gaussian shape normally occurring in column chromatography where it is known that axial dispersion is much more prominent than in countercurrent operation. Therefore, column efficiency is of more concern in 3W-ISMB than in SMB.
2.6 Nomenclature

\( A \)  
\text{Column cross section area [cm}^2\text{]}  

\( c_{F,i} \)  
\text{Feed concentration of component } i \text{ [g/l]}  

\( c_i \)  
\text{Concentration of component } i \text{ [g/l]}  

\( \Delta P \)  
\text{Pressure drop [bar]}  

\( \Delta P_j \)  
\text{Pressure drop in section } j \text{ [bar]}  

\( \Delta P_{\text{max}} \)  
\text{Maximum allowable pressure drop [bar]}  

\( H_i \)  
\text{Henry’s constant of component } i \text{ [-]}  

\( \dot{H}_i \)  
\text{Reduced Henry’s constant of component } i \text{ [-]}  

\( L \)  
\text{Column length [cm]}  

\( m_j \)  
\text{Dimensionless flow rate ratio in section } j \text{ [-]}  

\( m_j^D \)  
\text{Dimensionless flow rate ratio in dead volume of section } j \text{ [-]}  

\( \dot{m}_j \)  
\text{Combined dimensionless flow rate ratio in section } j \text{ [-]}  

\( \overline{m}_j \)  
\text{Effective dimensionless flow rate ratio in section } j \text{ [-]}  

\( P_{u_i} \)  
\text{Purity of outlet stream where component } i \text{ is collected [%]}  

\( Q \)  
\text{Volumetric flow rate [ml/min]}  

\( Q_j \)  
\text{Volumetric flow rate in section } j \text{ [ml/min]}  

\( T \)  
\text{Temperature \[°C\]}  

\( t_j^* \)  
\text{Duration of the substep associated to flow rate } Q_j \text{ [min]}  

\( t_{RI,i} \)  
\text{Retention time of component } i \text{ [min]}  

\( t_s^* \)  
\text{Duration of substep } s \text{ [min]}  

\( t_0 \)  
\text{Residence time of an unretained component [min]}  

\( u_j \)  
\text{Superficial velocity in section } j \text{ [cm/min]}  

\( V \)  
\text{Column volume [ml]}  

\( V_a \)  
\text{Dead volume between inlet manifold and column inlet [ml]}  

\( V_b \)  
\text{Dead volume between column outlet and outlet manifold [ml]}  

\( V_c \)  
\text{Dead volume between outlet manifold and inlet manifold [ml]}  

\( V_1^D \)  
\text{Overall dead volume [ml]}  

\( V_2^D \)  
\text{Dead volume of one module without connecting tubbing [ml]}  

\( v_i^j \)  
\text{Propagation velocity of species } i \text{ in section } j \text{ [cm/min]}  

\textbf{Greek Letters}  

\( \epsilon^* \)  
\text{Overall void fraction [-]}  

\( \lambda_F \)  
\text{Weighting factor for feed flow rate [-]}  

\( \lambda_S \)  
\text{Weighting factor for solvent consumption [-]}  

\( \lambda_t \)  
\text{Weighting factor for duration of the switching period [-]}  

\( \nu \)  
\text{Phase ratio [-]}  

\( \phi \)  
\text{Pressure drop factor in Darcy’s law [bar min cm}^{-2}\text{]}  

\( \varphi \)  
\text{Parameter in 3S-ISMB (0 \leq \varphi \leq 1) [-]}
Subscripts and Superscripts

A  Weakest retained component
B  Intermediately retained component
C  Strongest retained component
D  Dead volume
F  Feed
i  Component index (i=A,B,C)
j  Section index (j=0,1,2,3,4)
max  Maximum allowable
s  Substep index (s=,I,II)
3.1 Introduction

Simulated Moving Bed (SMB) Chromatography [8, 9] is a well established multi-column continuous binary separation process. Owing to its excellent performance as compared to batch chromatography, namely high purity levels at high productivity and low solvent consumption, SMB has become an important unit operation for the separation of enantiomers [5]. Since the need for expensive chiral stationary phases (CSP) is a major cost factor, there is a continuous effort into finding modified SMB schemes yielding higher productivities, i.e. higher throughput per unit time and unit volume of CSP [5].

The most successful modifications to conventional SMB are process schemes with non-constant operating conditions, i.e. processes wherein the switch time is divided into two or more substeps, which allows variation of the operating parameters in a stepwise manner and thus increases the number of degrees of freedom. In general the additional complexity hampers the design since simple short-cut design methods such as Triangle Theory [23] are no longer applicable. The increased complexity is, however, compensated by an increase in productivity. The most prominent examples of this class of operating modes are among

others VariCol (variation of the column configuration) [24], PowerFeed (variation of the internal and external flow rates) [25 26], partial feed/partial withdrawal (variation of feed and raffinate flow rates so as to keep $Q_I$, $Q_{II}$ and $Q_{IV}$ constant) [27], ModiCon (variation of the feed concentration to influence the migration velocities) [28], and intermittent SMB (I-SMB) which can be regarded as a special case of PowerFeed and is discussed in more detail in section [3.2.1].

Another straightforward method to reduce the number of columns is the adoption of a three section concept, i.e. the removal of the fourth section [31]. This modification results, however, in a highly diluted raffinate product and an increased solvent consumption due to the lack of a solvent recycle. Attempts to overcome these drawbacks were proposed by both Zang et al. and Lee et al. [32, 33, 34]; the former exploited the fact that the raffinate outlet consists essentially of pure solvent at the beginning of the switch period by recycling the corresponding part of the raffinate stream to section I [32], whereas the latter proposed a so-called raffinate rear-portion recycle [33, 34]. The rear-portion recycle concept is fundamentally different from all other concepts discussed so far, since the raffinate is only recovered at the beginning of the switching period and completely recycled to section I towards the end of the switching period. Thus, instead of recycling pure solvent, a stream that is rich in the weakly retained component is fed to section I. This concept works if the recycling period is initiated only when section I is already regenerated to a large extent and when it lasts for a relatively short fraction of the switching period. In other words, it has to be designed so as the front of the weakly retained component neither catches up the tail of the strongly retained component nor reaches the extract port. To the best of the author’s knowledge such an uncommon recycling regime is quite unique and he is not aware of any other processes making use of the same principle.

Despite the partial withdrawal of the raffinate, the process scheme proposed by Lee et al. is operated fully continuously and is thus likely to suffer from the influence of the port shift discontinuity in the same manner as conventional SMB in 1-1-1-1 configuration [22, 36]. However, incorporating the principle of raffinate rear-portion recycle into I-SMB allows for exploiting the benefits of both concepts, namely a reduced number of sections and the possibility of achieving high purity levels with only one column per section. Therefore, the thesis proposes for the first time a three column intermittent SMB process, termed 3C-ISMB, that is characterized by intermittent feed and withdrawal as well as by recycling of the weakly retained component from section III to section I.

In this chapter the new 3C-ISMB process is introduced and its performance is assessed in terms of productivity and solvent consumption against conventional I-SMB by means of a thorough simulation study. Furthermore, it is shown that 3C-ISMB can be designed by Triangle Theory, which is an important advantage compared to other modified SMB processes. Moreover, it is discussed how the new process scheme yields the same high purity levels as its four columns analogue, but at significantly higher productivity and comparable solvent consumption. Finally, the potential of the novel 3C-ISMB mode of operation is discussed, in light of the theoretical results reported; showing that 3C-ISMB
is a powerful alternative to other modified SMB processes, especially for separations requiring expensive stationary phase materials.

3.2 Background

In order to better understand the development of the new 3C-ISMB process described in section 3.3 it is worth reviewing briefly the I-SMB process (section 3.2.1). Furthermore, the extension of Triangle Theory to I-SMB design (section 3.2.2) is briefly reviewed, which will later be used for designing 3C-ISMB separations as well. This will be continued by defining the most common separation performance parameters that later enable the benchmarking of 3C-ISMB against conventional I-SMB (section 3.2.3). Finally, this section is concluded with a concise description of the mathematical model and numerical solution adopted in this thesis (section 3.2.4).

3.2.1 The conventional I-SMB process

The I-SMB process is commercially used, as originally patented by Nippon Rensui Corporation [29, 35] for sugar separations. Recently, our group studied the process in great detail [22, 30, 36] which demonstrated its potential for a wider range of applications, particularly for chiral separations under nonlinear chromatographic conditions. Figure 3.1 shows a scheme of conventional I-SMB consisting of four sections each comprising one chromatographic column. The switch time is divided into two substeps; in substep 1 the unit is operated as a standard SMB, however, without flow in section IV. In substep 2 all inlet and outlet ports are closed and the fluid is just circulated through the column train in order to adjust the relative position of the concentration fronts. It has been shown that I-SMB in 1-1-1-1 configuration doubles the productivity of 1-2-2-1 standard SMB whilst fulfilling the same high purity specifications [22, 30]. This is a result of the semi-continuous mode of operation which ensures that the leading edge of the more retained component (component A) has a large clearing from the raffinate port at the time of product withdrawal. Similarly the trailing edge of the weakly retained component (component B) is far from the extract port during the withdrawal phase, therefore also a high extract purity can be achieved. The continuously operated standard SMB in contrast, features much narrower gaps between the decisive edges of the compositions fronts, namely the front of A and the tail of B, which are much closer to the product ports, thus making dispersion cause a drop in purity. In order to counter the negative effects caused by dispersion, it is therefore necessary to better approximate the counter-current movement of the solid phase, i.e. to use a higher number of chromatographic columns per section. This is the reason why standard SMB units are usually operated with at least six columns, for example in 1-2-2-1 configuration.
Figure 3.1: Process scheme of closed loop intermittent simulated moving bed (I-SMB) chromatography. Feed and desorbent supply as well as withdrawal of the product streams raffinate and extract is conducted during in substep 1, whereas in substep 2 all inlet and outlet ports are closed. After the end of substep 2 the ports are switched in direction of the fluid flow and substep 1 is repeated.
3.2.2 Short-cut design method (Triangle Theory)

Conventional SMB processes are frequently designed by applying a powerful short-cut design method, the so-called "Triangle Theory" [23]. The key idea of that method is the introduction of dimensionless flow rate ratios $m_j$ defined as

$$m_j = \frac{Q_j t^* - V e^*}{V(1 - e^*)} \quad (3.1)$$

where $Q_j$ is the volumetric flow rate in section $j$, $t^*$ is the switching time, $V$ the column volume and $e^*$ the overall void fraction. Under linear conditions, it can be easily shown, that the constraints for complete separation and complete regeneration of the solid and fluid phase, respectively, read as:

$$H_A \leq m_I \quad (3.2a)$$
$$H_B \leq m_{II} \leq H_A \quad (3.2b)$$
$$H_B \leq m_{III} \leq H_A \quad (3.2c)$$
$$m_{IV} \leq H_B \quad (3.2d)$$

where $H_i$ are the Henry constants of component $i$. Constraints $3.2b$ and $3.2c$ define a triangular region of complete separation in the $(m_{II}, m_{III})$-plane, whereas constraints $3.2a$ and $3.2d$ define a rectangular region of complete regeneration in the $(m_I, m_{IV})$-plane. Under non-linear chromatographic conditions, the triangle gets distorted, but explicit equations for its boundaries are available for the common case of Langmuirian adsorption, which makes the theory still easy to use [23]. In fact, the SMB practitioner normally chooses an operating point in the $(m_{II}, m_{III})$- and the $(m_I, m_{IV})$-plane, afterward the switching time is fixed according to maximum pressure drop considerations. Finally, the four internal flow rates can be calculated from the $m$-values and the switching time. This easy to use and well-known design tool was extended to I-SMB by introducing average flow rates defined as

$$\hat{Q}_j = \alpha Q_j + (1 - \alpha) Q_{IV} \quad (j = I, II, III) \quad (3.3a)$$
$$\hat{Q}_{IV} = (1 - \alpha) Q_{IV} \quad (3.3b)$$

where $\hat{Q}_j$ is the average volumetric flow rate in section $j$ and $\alpha$ is the step ratio which can have values ranging from zero to one. It is worth noting, that the limit $\alpha = 1$ corresponds to a conventional three-zone SMB process. The adoption of average flow rates allows applying Triangle Theory simply by redefining the $m$-values as

$$m_j = \frac{\hat{Q}_j t^* - V e^*}{V(1 - e^*)} \quad (3.4)$$
Chapter 3. 3C-ISMB: Description & Comparative Assessment

| Column |
|-----------------|--------|
| A $[\text{cm}^2]$ | 0.166  |
| L $[\text{cm}]$   | 15     |
| $\epsilon^*$ [-] | 0.68   |
| $\Delta P_{\text{max}}$ [bar]$^a$ | 40     |

| Component |
|-----------------|--------|
| Bi-Langmuir Isotherm (+)-Tröger’s Base | (−)-Tröger’s Base |
| $a_{i,1}$ [-] | 1.56   | 3.99 |
| $b_{i,1}$ [L/g] | 0.0132 | 0.0107 |
| $a_{i,2}$ [-] | 0.304  | 0.986 |
| $b_{i,2}$ [L/g] | 0.136  | 0.601 |
| $k_{\text{bi},\text{av}}$ [1/s]$^b$ | 2.96   | 1.81 |
| $\epsilon_{bi}D_{\text{ax},i}/(\epsilon^* u)$ [m]$^c$ | $3.01 \times 10^{-4}$ |
| $\phi$ [bar min/cm$^2$]$^d$ | 0.1    |

$^a$ Maximum allowable pressure drop of the column.
$^b$ Product of mass transfer coefficient and specific surface.
$^c$ Coefficient to determine the dispersion coefficient, where $\epsilon_{bi}$ is the bed void fraction, $\epsilon^*$ the overall void fraction and $u$ the superficial velocity.
$^d$ Pressure drop coefficient in Darcy’s law, $\Delta P/L = \phi u$.

Table 3.1: Characteristics of the binary system (taken from [22] and determined for racemic Tröger’s Base in pure Ethanol on Chiralpak AD with a particle size of 20 µm).

Finally the optimal switching time $t^*$ and step ratio $\alpha$ are obtained by enforcing the condition that the pressure drop through the set of columns is always equal to its maximum permitted value, $\Delta P_{\text{max}}$; hence for the four section I-SMB one gets:

$$t^*_1-\text{SMB} = \frac{\phi L^2}{\Delta P_{\text{max}}} \sum_{j=1}^{IV} n_j (m_j(1 - \epsilon^*) + \epsilon^*)$$ (3.5a)

$$\alpha_{1-\text{SMB}} = \frac{\sum_{j=I}^{IV} n_j (m_j - m_{\text{IV}})(1 - \epsilon^*)}{\sum_{j=I}^{IV} n_j (m_j(1 - \epsilon^*) + \epsilon^*)}$$ (3.5b)

where $n_j$ is the number of columns in section $j$, $\phi$ is the pressure drop factor in Darcy’s law (see table 3.1) and $L$ is the column length. For more details on equations (3.3) to (3.5) the reader is referred to our previous publication on I-SMB [30].
3.2.3 Separation performance metrics

The key separation performance metrics for any chromatographic separation are the productivity ($PR$), the solvent consumption ($SC$) and the recovery of the component of interest. This thesis is focused on a chiral separation aiming at complete separation; in this scenario the recovery is by definition equal to one and thus only productivity and solvent consumption are discussed in the following.

The productivity of chromatographic separations is often given in terms of throughput or mass of product per unit time. For chiral separations where the cost of the stationary phase is decisive, this metric is further weighted with the volume or mass of stationary phase. Therefore, the productivity is defined as

$$PR = \frac{\alpha (Q_E c_{A,E} + Q_R c_{B,R})}{n_{col} V} \quad (3.6)$$

where $Q_E$ and $Q_R$ stand for the volumetric flow rate of extract and raffinate, $c_{A,E}$ ($c_{B,R}$) for the average concentration of the more (less) retained component in the extract (raffinate) and $n_{col}$ for the total number of columns. The step ratio $\alpha$ ($0 < \alpha < 1$) in equation (3.6) accounts for the semi-continuous operation of the herein discussed intermittent SMB processes.

The specific solvent consumption $SC$ is the second important performance metric of SMB separations and usually defined as

$$SC = \frac{Q_D + Q_F}{Q_E c_{A,E} + Q_R c_{B,R}} \quad (3.7)$$

where $Q_D$ and $Q_F$ are the volumetric desorbent and feed flow rate, respectively.

3.2.4 Modeling intermittent SMB processes

The model equations for any (modified) SMB process are obtained by combining single column models implementing proper port switching rules and using proper boundary conditions. In this thesis, the so-called transport-dispersive model was implemented as governing mass balance equation for the single columns [60]. This model is accounting for convection and axial dispersion in the fluid phase as well as mass transfer through a linear driving force model, i.e. the model equations read as

$$\epsilon^* \frac{\partial c_i}{\partial t} + (1 - \epsilon^*) \frac{\partial q_i}{\partial t} + u \frac{\partial c_i}{\partial z} = \epsilon_b D_{ax,i} \frac{\partial^2 c_i}{\partial z^2} \quad (3.8a)$$

$$\frac{\partial q_i}{\partial t} = a_v k_{s,i} (q_{i}^* - q_i) \quad (3.8b)$$

$$q_{i}^* = f_i(c) \quad (3.8c)$$

where $c_i$ and $q_i$ are the concentrations of component $i$ in the fluid and in the adsorbed phase, $t$ and $z$ are the time and space coordinates, $u$ is the superficial velocity, $\epsilon_b$ the
bed void fraction, \( D_{ax,i} \) the axial dispersion coefficient of component \( i \), \( a_v \) the specific surface area of the adsorbent particles, \( k_{a,i} \) the mass transfer coefficient of component \( i \), and \( q_i^* \) the equilibrium loading of component \( i \) which in this work is expressed through a Bi-Langmuir adsorption isotherm, i.e.

\[
q_i^* = f_i(c) = \frac{a_{i,1}c_i}{1 + b_{A,1}c_A + b_{B,1}c_B} + \frac{a_{i,2}c_i}{1 + b_{A,2}c_A + b_{B,2}c_B} \quad (i = A, B)
\]

where \( a_{i,k} \) and \( b_{i,k} \) are the parameters of the Bi-Langmuir model. For the sake of comparison with the work by Katsuo et al. on the separation of Tröger’s Base in pure Ethanol on Chiralpak AD, the model parameters given in [22] and listed in table 3.1 were used throughout this chapter.

In order to solve equation (3.8) numerically, the model was normalized and a first-order backward difference scheme was applied to discretize the space derivative which results in

\[
\frac{dc_i(\xi)}{d\tau} = -\left(\frac{c_i(\xi) - c_i(\xi - \Delta\xi)}{\Delta\xi}\right) + \overline{D}_i \left(\frac{c_i(\xi + \Delta\xi) - 2c_i(\xi) + c_i(\xi - \Delta\xi)}{\Delta\xi^2}\right) - \nu \frac{dq_i(\xi)}{d\tau}
\]

\[
\frac{dq_i(\xi)}{d\tau} = \overline{k}_{a,i}(q_i^*(\xi) - q_i(\xi))
\]

where \( \tau \) and \( \xi \) are the normalized time and space coordinates, \( \nu \) is the phase ratio, and \( \overline{D}_i \) and \( \overline{k}_{a,i} \) are the normalized axial dispersion coefficient and mass transfer coefficient of component \( i \). The normalized variables are defined as

\[
\tau = \frac{tu}{\epsilon^*L} \quad (3.11a)
\]
\[
\xi = \frac{z}{L} \quad (3.11b)
\]
\[
\nu = \frac{1 - \epsilon^*}{\epsilon^*} \quad (3.11c)
\]
\[
\overline{D}_i = \frac{\epsilon^*}{uL} \left(\frac{\epsilon^*D_{ax,i}}{\epsilon^*} - \frac{u\Delta z}{2\epsilon^*}\right) \quad (3.11d)
\]
\[
\overline{k}_{a,i} = \frac{\epsilon^*L}{u} k_{a,i} a_v \quad (3.11e)
\]

With reference to equation (3.11d) it is worth mentioning that \( \overline{D}_i \) for each section is obtained by multiplying the factor given in table 3.1 with the superficial velocity prevailing in the corresponding section (first term in equation (3.11d)), which is adjusted for numerical dispersion (second term in equation (3.11d)). In order to ensure a positive value of \( \overline{D}_i \), the minimal number of grid points \( n_{grid,\min} \) is given by

\[
n_{grid,\min} = \frac{L}{2\epsilon^* \epsilon^*D_{ax,i}}
\]

(3.12)
With the parameters given in table 3.1 a minimal number of 367 grid points is computed, upon adding a safety margin of 10 grid points the simulations were run with $\Delta \xi = 2.65 \cdot 10^{-3}$.

After implementing the Dankwerts boundary conditions, equation (3.10) was solved numerically with the CVODE solver which is included in the SUNDIALS package and based on backward differentiation [61].

3.3 The 3-column I-SMB process (3C-ISMB)

Although I-SMB has been shown to outperform standard SMB significantly [22, 30, 36], further studies on this promising process have revealed that roughly a quarter of the stationary phase is actually not actively used for the separation. On the one hand one of the four columns is completely idle during substep 1 and on the other hand the column of section I is almost completely regenerated at the end of substep 1, i.e. though being part of the column train during substep 2 this column does in fact not actively contribute to the separation during that fraction of the switching period. As a result, further enhancements are possible by exploiting the stationary phase more efficiently, e.g. by accommodating another separation zone and a third outlet stream to allow for three fraction separation [50] or by reducing the amount of stationary phase so as to increase the productivity in the case of binary separations. The present chapter deals with the latter objective and is aimed at demonstrating that a reduction from four to three sections is possible without compromising product purity and throughput by adapting the idea of recycling the weakly retained component from section III to section I. Thus a process scheme is obtained that requires as little as three columns when one sticks to a 1-1-1 configuration, hence the new process was termed "Three-column Intermittent Simulated Moving Bed (3C-ISMB)".

The actual separation in this novel 3C-ISMB process, is fully equivalent to the one in conventional I-SMB (section 3.2.1), i.e. it is also taking place in sections II and III. The only difference between 3C-ISMB and I-SMB resides in the regeneration of stationary and mobile phase, which is discussed and demonstrated below. As a result, the same design methods being applied for I-SMB separations can be used for designing 3C-ISMB, which is discussed in detail next (section 3.3.2). To conclude this section, the potential enhancement of the separation performance offered by the 3C-ISMB concept is discussed (section 3.3.3).
Figure 3.2: Process scheme of the three column intermittent simulated moving bed (3C-ISMB) process. In the first substep the unit is operated fully identical to I-SMB as described in figure 3.1 and also the second substep is analogous to I-SMB in the sense that neither inlet nor outlet streams are provided to the unit. The fundamental difference of 3C-ISMB to conventional I-SMB resides in the fact that no fourth column is used to regenerate the solvent. A stream containing the weakly retained component is directly recycled from section III to section I which is feasible because section I is almost completely regenerated at the end of substep 1. Thus it can be used for adsorbing the weakly retained component, i.e. the task devoted to section IV in conventional I-SMB.
3.3.1 Process description and comparison to I-SMB

With reference to figure 3.2 it is noted that the 3C-ISMB process is operated in substep 1 in exactly the same way as the standard four section I-SMB; whereas substep 2 consists of only three instead of four sections which results in recycling a stream containing the weakly retained component (component B) rather than pure solvent. It is worth pointing out that on the one hand substep 1 in 3C-ISMB is not only fully identical to substep 1 of I-SMB but also to classical 3-zone open loop SMB and substep 1 of 3-zone SMB with partial recycle (see section 3.2.1 and [33, 34]). Substep 2 on the other hand, combines the concepts of I-SMB and 3-zone SMB with partial recycle in a novel manner; i.e. all inlet and outlet ports are closed and the fluid is just circulated with identical flow rates in each section along the column train, which is analogous to I-SMB. For the sake of consistency, the volumetric flow rate during the second substep is denoted as $Q_{IV}$. However, it is worth underlining that there is no physical presence of a fourth section, in fact the classical functions of sections I and IV are combined within a single section of the 3C-ISMB unit. Moreover, it is worth mentioning that the lack of the fourth section and thus the recycling of the weakly retained component is similar to the concept of 3-zone SMB with partial recycle. This combination exploits the benefits of both I-SMB and 3-zone SMB with partial recycle in a very efficient manner; this allows for operating the process with only one column per section, thus yielding a significantly higher productivity as will be shown in section 3.3.3.

Recalling that section I in I-SMB is almost completely regenerated at the end of substep 1 allows using this section in substep 2 for adsorbing the weakly retained component, i.e. during substep 2 of 3C-ISMB its first section fulfills the classical function of the fourth zone in the corresponding four zone processes. Therefore, identical design conditions must be fulfilled (see section 3.3.2). As a consequence it is, within certain limits, possible to run the 3C-ISMB process under exactly the same conditions in terms of $m$-values or in terms of flow rates, switching time and step ratio as the corresponding I-SMB process. This will be further explored in sections 3.3.2 and 3.4 for the time being, that feature is just exploited so as to illustratively demonstrate the key difference between 3C-ISMB and I-SMB. This can be done either by comparing the space-time diagram resulting from the equilibrium theory solution for both processes or by looking at the simulated internal concentration profiles of both processes under identical operating conditions. Here the latter approach is followed since it gives a more realistic description as it allows accounting for dispersion and mass transfer resistance. It is, however, noted that the space-time diagram for 3C-ISMB is straightforwardly derived from figure 4 in [30].

Most conveniently, the internal concentration profiles are compared at three characteristic points in time, therefore figures 3.3a to 3.3c (3.3d to 3.3f) show the internal concentration profile of I-SMB (3C-ISMB) at the beginning of the switching time, at the end of substep 1 and the end of substep 2, respectively. Figures 3.3a and 3.3b clearly reflect the inefficient use of the stationary phase in I-SMB, i.e. the fourth section is idle during substep 1 (fig. 3.3a) and the first section is almost completely regenerated at the end of substep 1 (3.3b) as already mentioned above. At the beginning of substep 2 the fourth column
Figure 3.3: Simulated internal concentration profiles: (a) I-SMB at the beginning of the switching time, (b) I-SMB at the end of substep 1, (c) I-SMB at the end of substep 2, (d) 3C-ISMB at the beginning of the switching time, (e) 3C-ISMB at the end of substep 1, (f) 3C-ISMB at the end of substep 2. The greyed part illustrates either the section featuring stagnant flow (I-ISMB) or the non-existing section (3C-ISMB). The profiles were calculated using the system parameters given in table 3.1 and the operating parameter given in table 3.2 (Sim F).
is reconnected to the column train so as to regenerate the solvent which is then recycled to section I to flush out the remaining small amount of the strongly retained component (fig. 3.3c). In contrast, 3C-ISMB recycles the fluid directly from section III to section I, i.e. rather than using a fully regenerated fourth section to adsorb the weakly retained component, this task is carried out in section I. This procedure further ensures that any remaining amount of the strongly retained component is completely flushed out at the end of the switching period (fig. 3.3f). In other words, 3C-ISMB does no longer perform complete regeneration of solid and fluid phase, respectively, and therefore exploits the stationary phase in a more efficient manner as clearly shown in figures 3.3d to 3.3f. With reference to figures 3.3a and 3.3b it is further noted that the internal profiles with reference to the product collection ports at the beginning of substep 1 are unaffected by the new recycling scheme, hence the internal profiles at the end of substep 1 are also identical (figs. 3.3b and 3.3e). As a result, the 3C-ISMB process yields under identical operating conditions the same product purities as I-SMB, however, its more efficient usage of the stationary phase results in much higher productivity.

In the following section, it is shown that 3C-ISMB can be designed by applying the same modified Triangle Theory used previously for the design of I-SMB. The simple design of the 3C-ISMB process based on an easy to apply short-cut method is an important advantage of 3C-ISMB as compared to other processes with non-constant operating conditions.

3.3.2 Process Design

For linear chromatographic conditions it is straightforward to prove that Triangle Theory (see section 3.2.2) is not only valid for I-SMB but also for 3C-ISMB, i.e. equations (3.4) and (3.2) also apply to 3C-ISMB design. There is, however, a major difference in the meaning of constraint (3.2d); whilst it guarantees complete regeneration of the solvent in the case of I-SMB, in the case of 3C-ISMB the same constraint ensures that the recycled weakly retained component does not reach the outlet of section I within the duration of substep 2. This condition must be fulfilled so as to prevent pollution of the extract due to an inappropriate recycling policy. For the sake of clarity, it is worth mentioning that the other three constraints (3.2a) to (3.2c) have exactly the same physical meaning in both 3C-ISMB and I-SMB.

Although the same definition for the m-values apply for 3C-ISMB, the switch time $t^*$ and the step ratio $\alpha$ according to equations (3.5a) and (3.5b) are no longer optimal, since the overall pressure drop in substep 2 is smaller in 3C-ISMB as compared to I-SMB due to the smaller number of columns, i.e. the application of equations (3.5a) and (3.5b) would result in operating the unit below the maximum pressure drop. Taking the smaller pressure drop in substep 2 into account, the flow rate $Q_{IV}$ can be increased, which allows increasing $\alpha$ and decreasing $t^*$; hence equations (3.5a) and (3.5b) modify to
\[ t_{3C-ISMB}^* = \frac{\phi L^2}{\Delta P_{\text{max}}} \sum_{j=I}^{III} n_j (m_j(1 - \epsilon^*) + \epsilon^*) \] (3.13a)

\[ \alpha_{3C-ISMB} = \frac{\sum_{j=I}^{III} n_j (m_j - m_{IV})(1 - \epsilon^*)}{\sum_{j=I}^{III} n_j (m_j(1 - \epsilon^*) + \epsilon^*)} \] (3.13b)

which is directly obtained from equation (3.5) by setting \( n_{IV} = 0 \).

It is worth pointing out that the analysis above demonstrates validity of Triangle Theory for linear chromatographic conditions, its applicability for non-linear conditions is however still a working hypothesis that is tested and validated through numerical simulations in section 3.4. Moreover, the reader is reminded that the above analysis is based on equilibrium theory, i.e. it only proves that the optimal operating points in the operating parameter planes are under linear and ideal conditions identical for both 3C-ISMB and I-SMB. For real conditions where band broadening effects cause dispersed concentration fronts, a necessity for larger safety margins, especially with respect to the boundary of \( m_{IV} \), is expected and indeed shown in section 3.4.

3.3.3 Effect on separation performance

With the separation performance metrics given in section 3.2.3 and the equilibrium theory analysis discussed in the previous section, the benefits of 3C-ISMB regarding separation performance can now be discussed. For that purpose, it is worth first commenting on the superior performance of I-SMB as compared to conventional SMB before discussing the differences between 3C-ISMB and I-SMB.

When comparing SMB to I-SMB two approaches yielding the same conclusion are possible; namely comparing both processes in 1-1-1-1 configuration or comparing 1-1-1-1 I-SMB to 1-2-2-1 SMB [22, 36]. In the first case, both processes are subject to the same maximum internal flow rate constraint, however, the feed flow rate for SMB must be significantly smaller since the vertex of the triangle in the \((m_{II}, m_{III})\)-plane is, contrary to I-SMB, not accessible without compromising purity. In the latter case, both 1-1-1-1 I-SMB and 1-2-2-1 SMB can be operated close to the vertex, provided that the column efficiency is good enough. Therefore, essentially the same \( m \)-values can be used for both processes, however, owing to the fewer columns in I-SMB, the unit can be operated at higher flow rates, which compensates for the semi-continuous operation. As a result, both processes allow for the same throughput but the smaller number of columns in I-SMB reduces the denominator of equation (3.6); hence I-SMB doubles the productivity of SMB whilst guaranteeing the same high product purities. For more details the reader is referred to previous publications [22, 36].

Now, for comparing 3C-ISMB to I-SMB it is first assumed that both processes are operated at the same operating point in the \((m_{II}, m_{III})\)-plane, which corresponds to the second approach outlined above. Under that condition, the first substep of both processes is exactly identical, thus the raffinate and extract flow rates as well as the product stream
concentrations and the duration of substep 1 are the same. However, due to the fact that 3C-ISMB uses only three instead of four columns during substep 2, a higher recycling flow rate \( Q_{IV} \) can be applied which allows for decreasing the duration of substep 2. As a result the step ratio \( \alpha \) increases whilst the number of columns \( n_{col} \) decreases in equation (3.13b) and thus a significant gain in productivity is achieved. Moreover, since the first substep of both processes is exactly identical also the specific solvent consumption is the same for both I-SMB and 3C-SMB. It is however noted that the specific solvent consumption is strongly dependent on the difference of \( m_I \) and \( m_{IV} \), more specifically a safety margin in the \((m_I, m_{IV})\)-plane comes at the expense of solvent consumption but guarantees complete regeneration of mobile and stationary phase (SMB and I-SMB), i.e. it avoids pollution of the extract (3C-ISMB). Since, the need for a higher safety margin for \( m_{IV} \) (see section 3.3.2) is expected, one might have to accept a higher solvent consumption, a price well worth paying given the large gains in productivity.

3.4 Analysis of the cyclic steady state behavior

In the previous section it was demonstrated that 3C-ISMB separations are easy to design since the same modified version of Triangle Theory as being used for the design of I-SMB, i.e. equation (3.4), is applicable. Since a rigorous mathematical proof for the 3C-ISMB under nonlinear conditions is not possible and since band broadening effects need to be considered in order to judge on the performance of a real system, the working hypothesis that Triangle Theory for nonlinear conditions applies also to 3C-ISMB is tested by means of numerical simulations. In the case of I-SMB the applicability of Triangle Theory has already been demonstrated by following the same approach, i.e. by exploring a fine grid of operating points in the \((m_{II}, m_{III})\)-plane around the boundaries of the theoretical triangle, thus showing that the real region of complete separation for I-SMB essentially overlaps with the one predicted by Triangle Theory [22, 36]. In the following, it is aimed at (i) confirming the applicability of Triangle Theory for 3C-ISMB and (ii) comparing the separation performance of 3C-ISMB and I-SMB under real conditions by making use of the transport-dispersive model. For that purpose, the effect of varying the operating point in the \((m_{II}, m_{III})\)-plane at a fixed and rather robust operating point in the \((m_I, m_{IV})\)-plane (section 3.4.1) is explored so as to demonstrate applicability of Triangle Theory. The optimal operating point in the \((m_{II}, m_{III})\)-plane determined in this way is than fixed in order to explore the influence of the operating point in the \((m_I, m_{IV})\)-plane (section 3.4.2). This second part is aimed at answering the question whether the expected increase in solvent consumption is within an acceptable range. Finally, this part is closed by studying highly non-linear conditions (section 3.4.3).
3.4.1 Exploring the \((m_{II}, m_{III})\) plane

The regions of complete separation in the operating parameter plane for the standard SMB separation of a system subject to a Bi-Langmuir isotherm are readily calculated by applying the method developed by Migliorini et al. [62]. Although, the boundaries of these regions were derived for SMB and are based on the equilibrium theory model, i.e. a simplified model which neglects mass transfer resistance and axial mixing, Katsuo et al. showed that the vertex of the real region of complete separation for the I-SMB process is very well predicted by Triangle Theory [22, 36]. This was shown both experimentally and through simulations where a small region around the vertex of the theoretical triangle was screened applying an equilibrium-dispersive model for the same system being studied in this chapter.

Here a similar approach for both I-SMB and 3C-ISMB is followed, which is, however, more comprehensive in the sense that a more detailed model is used and that all relevant operating points in the \((m_{II}, m_{III})\)-plane are considered. More precisely, the operating point in the \((m_{I}, m_{IV})\)-plane was fixed at \((6.0, 1.22)\) and all operating points in the range \(1.4 \leq m_{II} < m_{III} \leq 5.0\) with a grid spacing of 0.04 were studied for total feed concentrations of 1, 5, 10, and 15 g/L, i.e. the same feed concentrations that were studied previously [22, 36]. For each operating point the switch time and the step ratio were determined through the minimum switch time design, i.e. equations (3.5) and (3.13) were applied for I-SMB and 3C-ISMB, respectively. Afterwards, the internal volumetric flow rates were computed and each operating point was simulated for 100 cycles in order to ensure cyclic steady state. Simulating many cycles for many operating points required parallelization and utilization of a high-performance computation cluster.

The results of these simulation studies are presented graphically in the operating parameter planes in figures 3.4 and 3.5 and are summarized in table 3.2. With reference to the graphical representation it is noted that the ideal triangle is given by the solid lines and all operating points in the \((m_{II}, m_{III})\)-plane yielding cyclic steady state product purities >99.9% for both product streams are indicated with a green point. The red (blue) points indicate operating points yielding only extract (raffinate) purities >99.9%, whereas the grey points represent the regions where no pure products are obtained.

The results for I-SMB shown in figure 3.4 demonstrate clearly the applicability of Triangle Theory for the design of conventional I-SMB. It is worth pointing out, that these results substantiate the conclusion drawn by Katsuo et al. [22, 36] in a more comprehensive manner. In those previous publications the validity of Triangle Theory for I-SMB was claimed after having shown that the real vertices of the triangles for total feed concentrations of 1, 5, 10, and 15 g/l essentially overlap with the vertices of the ideal triangle. Now, this analysis does not only demonstrate that the same results are obtained when using a more detailed model (transport-dispersive instead of equilibrium-dispersive) but also that the whole envelope of the region of complete separation for I-SMB is predicted extremely well by Triangle Theory.
Figure 3.4: Simulation based analysis of the purity levels achieved for conventional I-SMB for a fixed operating point in the \((m_I, m_{IV})\)-plane (filled black box) and total feed concentrations of (a) 1 g/l, (b) 5 g/l, (c) 10 g/l, and (d) 15 g/l. The solid lines indicate the boundaries of complete separation and regeneration according to Triangle Theory whereas all operating points yielding purities of at least 99.9% for both product streams are indicated with a green \(\bullet\)-symbol and the letters "E+R". Correspondingly, all operating yielding only an extract (raffinate) purity of at least 99.9% are marked with a red (blue) \(\bullet\)-symbol and the letter "E" ("R"). For the sake of completeness, all other operating points studied are indicated with a grey \(\bullet\)-symbol.
Figure 3.5: Simulation based analysis of the purity levels achieved for 3C-ISMB for a fixed operating point in the \((m_I, m_{IV})\)-plane and total feed concentrations of (a) 1 g/l, (b) 5 g/l, (c) 10 g/l, and (d) 15 g/l. The notation is given in the caption of figure 3.4.
### Table 3.2: Separation performance of the optimal operating points with respect to productivity for a fixed operating point in the \((m_I, m_{IV})\)-plane, i.e. the vertices of the real triangles for I-SMB and 3C-ISMB as shown in figures 3.4 and 3.5 as well as 3.8d and 3.9. The differences of productivity and solvent consumption are given in terms of \((PR_{3C-ISMB}/PR_{I-SMB} - 1)\) and \((SC_{3C-ISMB}/SC_{I-SMB} - 1)\).
More importantly, the conjectured hypothesis that Triangle Theory remains applicable for the design of the new 3C-ISMB process is confirmed by figure 3.5, which demonstrates clearly that the hypothesis is indeed correct, if a larger safety margin on $m_{IV}$ is imposed. For the sake of clarity, this point is further analyzed in the following section. For the time being, it is noted that the optimal operating points for 3C-ISMB and I-SMB are identical or at least very close to each other for all feed concentrations studied. However, the real triangles for 3C-ISMB as shown in figure 3.5 are smaller than those predicted by Triangle Theory and this effect becomes more prominent as the feed concentration increases. Furthermore, the boundary indicating the transition to impure raffinate is not affected by the removal of the fourth column, i.e. it still overlaps with the ideal boundary and thus also with the real boundary for conventional I-SMB. In fact, the sole reason for obtaining a smaller region of complete separation than predicted by the theory stems from the fact that the extract purity becomes prone to dispersion in the recycle stream, which no longer consists of pure solvent as in I-SMB. As a result, the real boundary in the $(m_{II}, m_{III})$-plane determining the extract purity shifts to the upper right hand side with respect to the ideal one. In other words, a clearing from the ideal boundary is required in cases where the extract pollution due to the recycle comes close to the threshold of 0.1%, i.e. when no further pollution due to dispersion in the central sections is tolerable. It is worth noting, that the ideal $m_{IV}$-boundary shifts downwards as the concentration increases, i.e. it approaches more and more the operating point which was fixed at $m_{IV} = 1.22$. Consequently, the shrinkage of the real triangle becomes more significant as the concentration increases; this point will be further clarified in section 3.4.2.

After having demonstrated the applicability of Triangle Theory for 3C-ISMB and having derived the real region of complete separations for I-SMB and 3C-ISMB, this section is concluded by comparing these two processes in terms of their separations performances, i.e. productivity and solvent consumption. For complete separation, equations (3.6b) and (3.7) reduce to

\[
PR = \frac{\alpha Q_{F} C_{F,\text{tot}}}{n_{\text{col}} V} \\
SC = \frac{Q_{D} + Q_{F}}{Q_{F} C_{F,\text{tot}}}
\]

which allow for straightforward comparison of the process performances. From figures 3.4 and 3.5 it is evident that the optimal operating points in terms of productivity, i.e. the vertices of the real regions of complete separation, are essentially identical for I-SMB and 3C-ISMB even in cases where the real region of complete separation for 3C-ISMB is smaller. In other words, one might have to accept a smaller region of complete separation when switching from I-SMB to 3C-ISMB, however, the lost subregion is hardly of practical relevance since it consists of operating points that are anyhow suboptimal.

The optimal operating points for each simulation study are given in table 3.2, which confirms the graphical observation, i.e. that the optimal operating point in the $(m_{II},$
m_{III})-plane for I-SMB and 3C-ISMB are either identical or at least very close to each other. For the sake of simplicity, the situation when identical optimal operating points are obtained is briefly discussed. In that case, both the feed flow rate as well as the desorbent flow rate are identical, i.e. both processes perform equally in terms of solvent consumption. However, since 3C-ISMB requires only three instead of four columns, it performs roughly 55% better in terms of productivity as compared to I-SMB. This gain in productivity is due to two reasons; (i) trivially the reduction of stationary phase at constant feed flow rate results as such in an increase of 33%, and (ii) the smaller number of columns in the unproductive substep 2 allows for higher flow rates during that period, thus the duration of substep 2 is shorter, or equivalently the step ratio $\alpha$ increases which yields an additional gain in productivity.

### 3.4.2 Exploring the ($m_I$, $m_{IV}$)plane

Since the shrinkage of the real 3C-ISMB triangle observed above becomes more significant as the $m_{IV}$-boundary moves closer to the chosen operating point, our expectation that 3C-ISMB requires a larger clearing from the $m_{IV}$-boundary than I-SMB seems to be confirmed. Therefore, it is worth studying this effect in more detail by fixing the operating point in the ($m_{II}$, $m_{III}$)-plane and exploring a fine grid of operating points in the ($m_I$, $m_{IV}$)-plane. In order to challenge the 3C-ISMB process the optimal ($m_{II}$, $m_{III}$)-values obtained above for I-SMB are used as fixed values and all operating points in the range $4.2 \leq m_I \leq 6.0$ and $0.22 \leq m_{IV} \leq m_{IV,\text{max}}$ with a grid spacing of 0.04 are explored, where $m_{IV,\text{max}} < m_{II}$ so as to guarantee positive volumetric flow rates in section II. Moreover, it is worth mentioning that all operating points are simulated for 400 cycles, since the carry over of the strongly retained component from section I to section III when operating in the non-complete stationary phase regeneration region is rather sluggish; hence there are cases where 100 cycles are not enough to achieve cyclic steady state.

The results are presented in figures 3.6 and 3.7 using the same notation as in section 3.4.1 for the sake of easy reference the fixed operating point used in the previous study is indicated with an open black box. The main conclusions are: (i) 3C-ISMB requires indeed a larger safety margin from the $m_{IV}$-boundary, as expected; (ii) the feasible region in the ($m_I$, $m_{IV}$)-plane becomes larger as the concentration increases; and (iii) Triangle Theory provides good guidelines for selecting the operating point in the ($m_I$, $m_{IV}$)-plane. Besides these general trends, some peculiarities can be observed that were rationalized by carefully inspecting the internal concentration profiles. Firstly, the feasible region for I-SMB at 1 g/l (fig. 3.6a) is rather small and both product purities fall below the threshold of $>99.9\%$ when $m_{IV}$ decreases to much. Moreover, no feasible operating point for 3C-ISMB is obtained at the optimal I-SMB operating point in the ($m_{II}$, $m_{III}$)-plane, i.e. both processes are prone to dispersion when operated under nearly linear conditions where the concentration fronts are less steep. Additionally, the observed decrease in purity as $m_{IV}$ decreases is a specific consequence of the intermittent operation of these processes. Given that the operating point in the ($m_{II}$, $m_{III}$)-plane is fixed, a decrease in $m_{IV}$ requires the composition front to move farther during substep 1, i.e. the front of
Figure 3.6: Simulation based analysis of the purity levels achieved for conventional I-SMB for a fixed operating point in the $(m_{II}, m_{III})$-plane and total feed concentrations of (a) 1 g/l, (b) 5 g/l, (c) 10 g/l, and (d) 15 g/l. The notation is given in the caption of figure 3.4, additionally an unfilled black box indicates the operating points used for deriving figure 3.4.
Figure 3.7: Simulation based analysis of the purity levels achieved for 3C-ISMB for a fixed operating point in the ($m_{II}$, $m_{III}$)-plane and total feed concentrations of (a) 1 g/l, (b) 5 g/l, (c) 10 g/l, and (d) 15 g/l. The notation is given in the caption of figure 3.6.
the strongly retained component comes closer to the raffinate port during the product withdrawal period. In other words, I-SMB and 3C-ISMB approach more and more the behavior of a standard three-zone SMB unit and start to suffer from the drawbacks of a 1-1-1 SMB unit. In addition, the product streams become more diluted, i.e. the average product concentrations decrease whilst the decisive edges of the internal concentration profiles are essentially unaffected and thus become relatively more important. Secondly, whilst the results of the 10 g/l case (figs. 3.6c and 3.7c) reflect exactly the general trends and correspond to the expectations, the feasible region of the 15 g/l case is again slightly smaller; which is attributed to the fact that the purities of the reference cases, i.e. I-SMB Sim C and Sim D in table 3.2 were slightly different. More precisely, Sim C yielded product purities of 100.0% and 99.99% for raffinate and extract and therefore some pollution due to the choice of $m_I$ and $m_{IV}$ is still tolerable without violating the threshold.

To conclude this section, it is noted with reference to figure 3.7d, that the operating point in the $(m_I, m_{IV})$-plane chosen for Sim D lies outside the feasible region which might explain why the real triangle in figure 3.5d was relatively small. The previous exercise is therefore repeated for three additional $m_{IV}$ values. The corresponding results shown in figure 3.8 demonstrate without any doubt, that the whole triangle is accessible as long as the operating point in the $(m_I, m_{IV})$-plane is chosen properly, i.e. with a certain clearing from the ideal $m_{IV}$-boundary.

### 3.4.3 Exploring highly non-linear conditions

In this last analysis, the hypothesis that Triangle Theory is applicable for I-SMB and 3C-ISMB is challenged by studying heavily non-linear conditions. For that purpose the feed concentrations was increased to 200 g/l and the range of operating points increased to $1.0 \leq m_{II} < m_{III} \leq 5.0$ at constant $m_I$-value but a decreased $m_{IV}$-value of 0.47. It is worth noting that this feed concentration is way above the solubility limit of Tröger’s Base in Ethanol, nonetheless it serves the purpose aimed at. Furthermore, the same strategy for exploring the $(m_I, m_{IV})$-plane was applied and the full-set of results is presented in figure 3.9. Based on these observations it is definitely concluded, that (i) Triangle Theory is applicable for both I-SMB and 3C-ISMB, (ii) the process performance in terms of purities and robustness converge as the degree of nonlinearity increases and (iii) both processes should be operated close to the solubility limit so as to minimize negative influences of band broadening.

### 3.4.4 Optimizing Productivity and Solvent Consumption

Exploiting the results from the previous analyses one can finally compare the performance of 3C-ISMB and I-SMB at the corresponding optimal operating point with respect to productivity and solvent consumption. The optimal operating point in terms of productivity corresponds to the vertex of the real triangle, i.e. the operating point that has been kept
Figure 3.8: Influence of the $m_{IV}$ safety margin on the real region of complete separation for 3C-ISMB. The safety margin steadily increases from figure (a) to (d) and the $m_{IV}$-value is indicated in each figure. The same notation as in figure 3.4 applies.
Figure 3.9: Simulation based analysis of the purity levels achieved for I-SMB (a and c) and 3C-ISMB (b and d) under highly non-linear chromatographic conditions, i.e. at a total feed concentration of 200 g/l. The same notation as in figure 3.4 applies.
fixed when exploring the \((m_I, m_{IV})\)-plane. Therefore, the overall optimum is readily obtained from figures 3.6 and 3.7 as well as 3.9c and 3.9d as it corresponds to the vertex of the feasible region in the \((m_I, m_{IV})\)-plane, i.e. the operating point that minimizes the difference between \(m_I\) and \(m_{IV}\). The optimal operating points are listed in table 3.3 and their performances are illustrated graphically in figure 3.10. It is noted that no comparison for the lowest feed concentration was made, since no feasible operating point in the \((m_I, m_{IV})\)-plane was found for the chosen operating point in the \((m_{II}, m_{III})\)-plane.

This concluding set of data summarizes the conclusions made previously, particularly (i) the higher productivity of 3C-ISMB as compared to I-SMB, and (ii) the applicability of Triangle Theory for 3C-ISMB design when using a larger safety margin from the \(m_{IV}\)-boundary. It is worth mentioning that the need for slightly lower \(m_{IV}\)-values leads to an increase in solvent consumption between 5.5% and 9.6%, however, a lower \(m_{IV}\)-value also allows for a shorter duration of the non productive substep 2. As a result, the gain in productivity when operating both processes at their optimal operating point is even higher as compared to the case where both processes were run at a rather robust operating point in the \((m_I, m_{IV})\)-plane (see table 3.2).
Table 3.3: Separation performance of the optimal operating points maximizing productivity and minimizing solvent consumption. The differences of productivity and solvent consumption are given in terms of $(PR_{3C-ISMB}/PR_{1-SMB} - 1)$ and $(SC_{3C-ISMB}/SC_{1-SMB} - 1)$.
3.5 Practical considerations

In the previous section it has been demonstrated that the adoption of the 3C-ISMB results in significant improvements of the separation performance as compared to I-SMB assuming that both processes are operated with columns of the same length. Interestingly, these gains are achievable by simply modifying the operating conditions, i.e. any SMB unit being in use today can potentially run the novel process without the need for investing in new hardware such as additional pumps or valves. Moreover, the step ratio in 3C-ISMB comes relatively close to 0.5 when applying the minimum switch time constraint. Therefore, one might consider relaxing this constraints so as to enforce a step ratio of 0.5, which would allow transforming a six column SMB plant into two parallel operating 3C-ISMB units with alternating substep sequence. In a continuous production environment, this strategy might be desired so as to omit buffer tanks before downstream processing. In practice such a parallelization strategy requires to prolong the duration of substep 1 by lowering the internal flow rates so as to keep the $m$-values constant. Although this policy was not studied in detail, it is rather obvious that it will compromise productivity whilst purity will remain constant or even increase. In order to assess the effect on productivity, $PR$ for all runs tabulated in tables 3.2 and 3.3 was also calculated for a fixed $\alpha$ of 0.5 and in good approximation a linear relationship between $\Delta \alpha = 0.5 - \alpha_{opt}$ and the loss in productivity was found, i.e. for Sim E one would loose 1.8% (13.82%) in the case of 3C-ISMB (I-SMB) whereas in Sim Eopt the corresponding loss would be 18.0% (30.2%). In other words, the I-SMB process, which has usually an optimal step ratio far below 0.5, is not well suited for adopting the parallelization strategy proposed above. In contrast, the optimal step ratio of 3C-ISMB is often quite close to 0.5, which allows adopting parallelization without too much compromising the productivity of the individual units. The possibility for parallelization is clearly another important benefit offered by 3C-ISMB.

It is worth further pointing out that the methodology applied in this study allows mainly conclusions concerning retrofits, i.e. how the performance of existing units can be improved by applying a different and new mode of operation. However, when building new plants additional degrees of freedom are available and the column length will become an optimization variable. Under these circumstances the differences in process performance might be different, possibly less favorable. Further exploring this point would require a full optimization including also standard SMB and relaxing the maximum pressure drop constraint, which is clearly beyond the scope of this study.

3.6 Conclusions

In this chapter, a novel three-column semi-continuous chromatographic process for binary separation termed three-column intermittent simulated moving bed (3C-ISMB) process has been presented. The state of the art was reviewed in detail (section 3.1) and it was shown that the proposed 3C-ISMB scheme combines two known concepts, namely
intermittent operation and recycling of the weakly retained component, in a novel manner and thus exploits the benefits of both concepts (section 3.3).

In an extensive simulation study, it was shown that 3C-ISMB can be easily designed by the well-known Triangle Theory and that its implementation results in an increase of productivity by as much as 60% as compared to I-SMB without significantly sacrificing solvent consumption. Given that I-SMB was shown to outperform standard SMB by a factor 2 [22], it can thus be concluded that changing from the still widely applied standard SMB to 3C-ISMB would boost productivity by a factor three.

An additional advantage of 3C-ISMB is the fact that the process can be designed by a slightly modified version of Triangle Theory. The latter is a well-known short-cut design tool being regularly applied by SMB practitioners both in academia and industry. Therefore, the modified process is likely to be easily understood and accepted as valuable improvement by the SMB community. Furthermore, this makes the design of 3C-ISMB processes much simpler as compared to other SMB schemes using non-constant operating conditions which usually require sophisticated optimization strategies.

In the next chapter, the 3C-ISMB concept is validated experimentally by implementing it for the separation of Tröger’s Base in pure Ethanol on Chiralpak AD, i.e. the system treated theoretically in the present chapter.

### 3.7 Nomenclature

- **A**: Column cross section area [cm²]
- **a_v**: Specific surface of the adsorbent particles [cm⁻¹]
- **a_i,1, a_i,2**: Parameters in Bi-Langmuir isotherm [-]
- **b_i,1, b_i,2**: Parameters in Bi-Langmuir isotherm [l g⁻¹]
- **c_{e,i}**: Concentration of component i in external stream e [g l⁻¹]
- **c_{F,tot}**: Total feed concentration [g l⁻¹]
- **c_i**: Concentration of component i [g l⁻¹]
- **D_{ax,i}**: Axial dispersion coefficients of component i [cm² s⁻¹]
- **D_{i}**: Dimensionless axial dispersion coefficients of component i [-]
- **ΔP**: Pressure drop [bar]
- **ΔP_{max}**: Maximum allowable pressure drop [bar]
- **Δz**: Grid length in discretized mass balance [cm]
- **f_i(c)**: Isotherm of component i [g l⁻¹]
- **H_i**: Henry’s constant of component i [-]
- **k_{s,i}**: Mass transfer coefficient of component i [s⁻¹]
- **k_{a,i}**: Dimensionless mass transfer coefficient of component i [-]
- **L**: Column length [cm]
- **m_j**: Dimensionless flow rate ratio in section j [-]
- **n_{col}**: Total number of columns [-]
- **n_{grid,min}**: Minimum number of grid points [-]
- **n_j**: Number of columns in section j [-]
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
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</thead>
<tbody>
<tr>
<td>PR</td>
<td>Productivity ([\text{g l}^{-1} \text{ h}^{-1}])</td>
</tr>
<tr>
<td>(Q_e)</td>
<td>Volumetric flow rate of external stream (e) ([\text{ml min}^{-1}])</td>
</tr>
<tr>
<td>(Q_j)</td>
<td>Volumetric flow rate in section (j) ([\text{ml min}^{-1}])</td>
</tr>
<tr>
<td>(\bar{Q}_j)</td>
<td>Average volumetric flow rate in section (j) ([\text{ml min}^{-1}])</td>
</tr>
<tr>
<td>(q_i)</td>
<td>Adsorbed phase concentration ([\text{g l}^{-1}])</td>
</tr>
<tr>
<td>(q^*_i)</td>
<td>Adsorbed phase concentration at equilibrium with the fluid phase ([\text{g l}^{-1}])</td>
</tr>
<tr>
<td>SC</td>
<td>Solvent consumption ([\text{l g}^{-1}])</td>
</tr>
<tr>
<td>(t)</td>
<td>Time coordinate ([\text{min}])</td>
</tr>
<tr>
<td>(t^*)</td>
<td>Switching time ([\text{min}])</td>
</tr>
<tr>
<td>(u)</td>
<td>Superficial velocity ([\text{cm min}^{-1}])</td>
</tr>
<tr>
<td>(V)</td>
<td>Column volume ([\text{ml}])</td>
</tr>
<tr>
<td>(z)</td>
<td>Axial coordinate ([\text{cm}])</td>
</tr>
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</table>

**Greek Letters**

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\alpha)</td>
<td>Step ratio ((0 \leq \alpha \leq 1)) [-]</td>
</tr>
<tr>
<td>(\Delta \xi)</td>
<td>Dimensionless grid length in discretized mass balance [-]</td>
</tr>
<tr>
<td>(\epsilon^*)</td>
<td>Overall void fraction [-]</td>
</tr>
<tr>
<td>(\epsilon_b)</td>
<td>Bed void fraction [-]</td>
</tr>
<tr>
<td>(\nu)</td>
<td>Phase ratio [-]</td>
</tr>
<tr>
<td>(\xi)</td>
<td>Dimensionless axial coordinate [-]</td>
</tr>
<tr>
<td>(\tau)</td>
<td>Dimensionless time [-]</td>
</tr>
<tr>
<td>(\phi)</td>
<td>Pressure drop factor in Darcy’s law ([\text{bar min cm}^{-2}])</td>
</tr>
</tbody>
</table>

**Subscripts and Superscripts**

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>3C-ISMB</td>
<td>Three-column intermittent simulated moving bed</td>
</tr>
<tr>
<td>A</td>
<td>Weak retained component</td>
</tr>
<tr>
<td>B</td>
<td>Strong retained component</td>
</tr>
<tr>
<td>D</td>
<td>Desorvent</td>
</tr>
<tr>
<td>E</td>
<td>Extract</td>
</tr>
<tr>
<td>(e)</td>
<td>Index for external stream ((e=D,E,F,R))</td>
</tr>
<tr>
<td>F</td>
<td>Feed</td>
</tr>
<tr>
<td>(i)</td>
<td>Component index ((i=A,B))</td>
</tr>
<tr>
<td>I-SMB</td>
<td>Intermittent simulated moving bed</td>
</tr>
<tr>
<td>(j)</td>
<td>Section index ((j=I,II,III,IV))</td>
</tr>
<tr>
<td>max</td>
<td>Maximum allowable</td>
</tr>
<tr>
<td>R</td>
<td>Raffinate</td>
</tr>
</tbody>
</table>
4

Three column intermittent simulated moving bed chromatography: Experimental implementation for the separation of Tröger’s Base

4.1 Introduction

Three column intermittent simulated moving bed (3C-ISMB) chromatography refers to a modification of the intermittent simulated moving bed (I-SMB) process, which has been patented [83] and analyzed theoretically in chapter 3. The conventional I-SMB process [29, 30, 35] itself is a modification to classical SMB chromatography [5, 8, 9] that was previously shown to significantly outperform SMB in terms of productivity [22, 36]. Despite the enhanced productivity of I-SMB with respect to SMB, a careful analysis has recently revealed that roughly a quarter of the adsorbent being used in I-SMB is actually not active in separating the feed mixture. To be more specific, section IV is completely idle for a relatively large fraction of the switching period, and section I is almost completely regenerated at the end of substep 1. This opens the way for two possible optimization strategies: (i) making use of the surplus adsorbent to accommodate

an additional separation zone so as to extend the field of possible applications by enabling
three fraction I-SMB separations (see chapter 2), and (ii) enhancing the productivity of
binary separations by removing the inactive fraction of the adsorbent in such a way that
the product purities are not compromised. The 3C-ISMB process is a powerful realization
of the second strategy, as theoretically demonstrated in the chapter 3 where substantial
improvements in terms of productivity were reported. The major differences between
I-SMB and 3C-ISMB will be discussed in more detail later (see section 4.2.1) where
the findings of chapter 3 will be summarized so as to demonstrate, how the 3C-ISMB
technology enables a reduction of the total number of columns to as little as three, without
compromising product purities.

The present contribution will be focused on the experimental implementation of the 3C-ISMB
technology and the comparison of 3C-ISMB with I-SMB by studying the separation
of Tröger’s Base enantiomers in pure ethanol on Chiralpak AD™. Thus, this chapter
is aiming at confirming the theoretically derived improvements of chapter 3 through a
thorough experimental study where the experimental performance of 3C-ISMB and I-SMB
will be directly compared in terms of product purity, productivity, and solvent
consumption.

This direct experimental comparison will be facilitated by switching the operation mode
from I-SMB to 3C-ISMB after attaining cyclic steady state. More precisely, each experi-
ment will be designed by Triangle Theory and accordingly started up in I-SMB mode until
cyclic steady state is reached. Afterwards, it will be continued in 3C-ISMB mode, which
will demonstrate that the cyclic steady state is essentially not affected by the change in
operating conditions. In other words, the same high purity levels are maintained, how-
ever, at a reduced amount of stationary phase and higher volumetric flow rates, i.e. at
substantially higher productivity. It is worth pointing out that this experimental study
is by design restricted to the assumption that both processes are operated with the same
column length, thus representing a typical case of retrofitting where the performance of
an existing set-up is enhanced simply by changing the operating conditions without the
need for new hardware.

In conclusion, this chapter will on the one hand experimentally confirm the previously
reported benefits of 3C-ISMB, namely (i) substantial improvements in terms of produc-
tivity with respect to I-SMB whilst maintaining the same high purity levels, and (ii) the
applicability of Triangle Theory for 3C-ISMB design. On the other hand, the simplic-
ity of experimental implementation on existing units will be illustrated by showing that
switching from I-SMB to 3C-ISMB can be quickly realized within the same experimental
run.
CHAPTER 4. 3C-ISMB: EXPERIMENTAL IMPLEMENTATION

4.2 Background

4.2.1 From I-SMB to 3C-ISMB

The conventional I-SMB process is characterized by (i) a division of the switching period $t^*$ into two substeps, and (ii) the employment of four sections, each consisting of only one chromatographic column $[29, 30]$. In substep 1 the feed and the mobile phase (desorbent) are introduced between sections II and III and into section I, respectively, whereas the extract (containing the strongly retained component A) is withdrawn between sections I and II and the raffinate (containing the weakly retained component B) is collected from section III. Noteworthy, section IV is not used during substep 1, i.e. the volumetric raffinate flow rate equals the internal volumetric flow rate of section III. In substep 2 all inlet and outlet ports are closed, section IV is reconnected to the column train in order to adsorb the weakly retained component, and the fluid is circulated at constant flow rate through the column train so as to adjust the relative position of the concentration fronts. It is worth mentioning that the introduction of average volumetric section flow rates allows demonstrating the equivalence of I-SMB and classical SMB $[30]$. Therefore, the same design methods (Triangle Theory) $[23]$ are applicable and each section of the I-SMB fulfills the same role as the corresponding section in an equivalent SMB unit, particularly the mobile and the stationary phase are regenerated in section IV and I, respectively.

Analogous to I-SMB, the switch time in 3C-ISMB is also divided into two substeps; the first one being identical in both processes. The key feature of the new 3C-ISMB process resides, however, in the combination of the classical functions of sections I and IV within a single section, i.e. instead of using a completely regenerated fourth section in substep 2 to adsorb component B as in I-SMB, the stream leaving section III and containing component B is directly recycled to section I. Adsorption of component B now takes place in section I which is feasible since this section is almost fully regenerated at the end of substep 1. As a result, 3C-ISMB is operated throughout the whole switching period with only three sections each comprising only one chromatographic column. The smaller number of columns in substep 2 is beneficial in two manners; on the one hand it allows saving stationary phase material, which is particularly important for chiral separations requiring very expensive stationary phases. On the other hand, fewer columns reduce the overall pressure drop and thus allow for higher internal flow rates without violating pressure drop constraints, which shortens the duration of the non productive second step. Chapter 3 demonstrated through a comprehensive set of simulations that the full exploitation of the advantages of 3C-ISMB results in an increase in productivity (defined as throughput per unit time and unit volume of stationary phase) by as much as 60% with respect to the corresponding I-SMB process. It is worth pointing out, that this increase in productivity is achievable without compromising purity, but usually a relatively small price in terms of solvent consumption has to be paid. For more details on the 3C-ISMB process, its design through Triangle Theory, and the theoretical comparative assessment, the reader is referred to section 4.2.3 and chapter 3.
4.2.2 Adsorption Isotherm

The system studied in this work, i.e. Tröger’s Base enantiomers in pure ethanol on Chiralpak AD™, has been studied previously by Katsuo et al. [22, 36, 59] and is known to follow a Bi-Langmuir adsorption isotherm, i.e.

\[ q_i = \frac{a_{i,1} c_i}{1 + b_{A,1} c_A + b_{B,1} c_B} + \frac{a_{i,2} c_i}{1 + b_{A,2} c_A + b_{B,2} c_B} \quad (i = A, B) \]  

(4.1)

Under linear chromatographic conditions, i.e. diluted feed concentrations, the adsorption can be described by Henry’s law where the Henry’s constants \( H_i \) are given by

\[ H_i = a_{i,1} + a_{i,2} = \frac{\epsilon^* t_{R,i} - t_0}{t_0} \quad (i = A, B) \]  

(4.2)

where \( t_{R,i} \) is the retention time of solute \( i \) (i=A,B) and \( t_0 \) is the residence time of an unretained component. Therefore, the Henry’s constant can be easily measured whilst the determination of the equilibrium constants \( b_{i,1} \) and \( b_{i,2} \) is relatively cumbersome.

In this work only the Henry’s constants were measured, which slightly differed from the data published by Katsuo et al. [22, 36] due to usage of a different batch of stationary phase material. Therefore the values \( a_{i,1} \) and \( a_{i,2} \) reported in [22, 36] were scaled so as to match the determined Henry’s constants, whereas the same values for \( b_{i,1} \) and \( b_{i,2} \) as in [22, 36] were assumed. The system characteristics are summarized in table 4.1.

4.2.3 Design of conventional I-SMB and 3C-ISMB separations

Conventional SMB processes are frequently designed by applying a powerful short-cut design method, the so-called ”Triangle Theory” [23]. The key idea of that method is the introduction of four dimensionless flow rate ratios \( m_j \) defined as

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

(4.3)

where \( Q_j \) is the flow rate in section \( j \), \( t^* \) is the switch time, \( V \) the column volume and \( \epsilon^* \) the overall void fraction. This transformation leads to a four-dimensional operating parameter space that can be best represented as two 2D operating parameter planes, i.e. the \((m_I, m_{IV})\)-plane and the \((m_{II}, m_{III})\)-plane. Under linear conditions the regions of complete separation are a triangle and a rectangle in the \((m_{II}, m_{III})\)- and \((m_I, m_{IV})\)-plane, respectively, which are defined by the following inequalities depending only on the Henry’s constants, i.e. \( H_B \leq m_{II} < m_{III} \leq H_A \) and \( m_{IV} \leq H_B < H_A \leq m_I \). Under non-linear chromatographic conditions, the triangle gets distorted, but for many practically relevant isotherms explicit equations for its boundaries are available, which makes the theory still easy to use [23, 64]. For the case of a Bi-Langmuir isotherm, as this work, the more general mathematical procedure developed by Migliorini et al. [62] has to be adopted to calculate the boundaries of the regions of complete separation.

Chapter 3 demonstrated that the introduction of average internal flow rates, defined as
allows for applying Triangle Theory also for the design of 3C-ISMB and I-SMB processes simply by redefining the \( m \)-values accordingly. As a result, the operating conditions for these processes are easily obtained by choosing an appropriate point in the operating parameter planes. Afterwards, the step ratio \( \alpha \) and the switch time as well as the internal flow rates are readily derived from the maximum pressure drop limitation. For the sake of brevity and completeness the general design equations for I-SMB and 3C-ISMB units with negligible extra-column dead volume and negligible pressure drop over the latter are given in the top part of tables 4.2 and 4.3. For more details the reader is referred to chapter 3. How to account for extra-column dead volume is discussed in section 4.3.1.

\[
\begin{align*}
\dot{Q}_j &= \alpha Q_j + (1 - \alpha)Q_{IV} \quad (j = I, II, III) \quad (4.4a) \\
\dot{Q}_{IV} &= (1 - \alpha)Q_{IV} \quad (4.4b)
\end{align*}
\]

allows for applying Triangle Theory also for the design of 3C-ISMB and I-SMB processes simply by redefining the \( m \)-values accordingly. As a result, the operating conditions for these processes are easily obtained by choosing an appropriate point in the operating parameter planes. Afterwards, the step ratio \( \alpha \) and the switch time as well as the internal flow rates are readily derived from the maximum pressure drop limitation. For the sake of brevity and completeness the general design equations for I-SMB and 3C-ISMB units with negligible extra-column dead volume and negligible pressure drop over the latter are given in the top part of tables 4.2 and 4.3. For more details the reader is referred to chapter 3. How to account for extra-column dead volume is discussed in section 4.3.1.

<table>
<thead>
<tr>
<th>Column</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( A ) ([\text{cm}^2])</td>
<td>0.166</td>
</tr>
<tr>
<td>( L ) ([\text{cm}])</td>
<td>15</td>
</tr>
<tr>
<td>( \epsilon^* ) ([-])</td>
<td>0.68</td>
</tr>
<tr>
<td>( \Delta P_{\text{max}} ) ([\text{bar}]^{a})</td>
<td>40</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Component</th>
<th>(+)-Tröger’s Base</th>
<th>(-)-Tröger’s Base</th>
</tr>
</thead>
<tbody>
<tr>
<td>( a_{i,1} ) ([-])</td>
<td>1.69</td>
<td>4.16</td>
</tr>
<tr>
<td>( b_{i,1} ) ([l/g])</td>
<td>0.0132</td>
<td>0.0107</td>
</tr>
<tr>
<td>( a_{i,2} ) ([-])</td>
<td>0.33</td>
<td>1.03</td>
</tr>
<tr>
<td>( b_{i,2} ) ([l/g])</td>
<td>0.136</td>
<td>0.601</td>
</tr>
<tr>
<td>( k_s a_v ) ([1/s])^{b}</td>
<td>2.96</td>
<td>1.81</td>
</tr>
<tr>
<td>( \epsilon_b D_{ax,i}/(\epsilon^* u) ) ([\text{m}]^c)</td>
<td>(3.01 \times 10^{-4})</td>
<td></td>
</tr>
<tr>
<td>( \phi_c ) ([\text{bar min/ml}]^d)</td>
<td>5.53</td>
<td></td>
</tr>
<tr>
<td>( \phi_t ) ([\text{bar min/ml}]^e)</td>
<td>13.15</td>
<td></td>
</tr>
</tbody>
</table>

\({}^a\) Maximum allowable pressure drop of the column as specified by the manufacturer, which is in fact understood as maximum total allowable pressure. Hence, the maximum allowable pressure drop of the column train is the same as the one specified for a single column.

\({}^b\) Product of mass transfer coefficient and specific surface.

\({}^c\) Coefficient to determine the dispersion coefficient, where \( \epsilon_b \) is the bed void fraction, \( \epsilon^* \) the overall void fraction and \( u \) the superficial velocity.

\({}^d\) Pressure drop coefficient of the column, \( \Delta P = \phi_c Q \).

\({}^e\) Pressure drop coefficient of the tubing connecting outlet and inlet manifold, \( \Delta P = \phi_t Q \).

Table 4.1: Characteristics of the binary model system.
### Table 4.2: Design equations for I-SMB for negligible dead volume and lab scale plant where dead volume and pressure drop along the dead volume has to be accounted for.

<table>
<thead>
<tr>
<th>m-values</th>
<th>I-SMB</th>
<th>no dead volume</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( m_j = \frac{\dot{Q}<em>i t^* - V</em>{c*}}{V(1-\epsilon^*)} )</td>
<td>( m_j = \frac{\dot{Q}<em>i t^* - V</em>{c*} - V_D}{V(1-\epsilon^*)} )</td>
</tr>
<tr>
<td>switch time</td>
<td>( t^* = \frac{\phi c V_D}{\Delta P_{\text{max}}} \sum_{j=I}^{IV} n_j (m_j(1-\epsilon^<em>) + \epsilon^</em>) )</td>
<td>( t^* = \frac{\phi c V}{\Delta P_{\text{max}}} \sum_{j=I}^{IV} n_j (m_j(1-\epsilon^<em>) + \epsilon^</em>) + \frac{\phi c V_D}{\Delta P_{\text{max}}} [(2m_{II} + m_{IV})(1-\epsilon^<em>) + 3\epsilon^</em> + 3V_D] )</td>
</tr>
<tr>
<td>step ratio</td>
<td>( \alpha = \frac{\sum_{j=II}^{III} n_j (m_j - m_{IV})(1-\epsilon^<em>)}{\sum_{j=I}^{IV} n_j (m_j(1-\epsilon^</em>) + \epsilon^*)} )</td>
<td>( \alpha = \frac{\phi c \sum_{j=II}^{III} (m_j - m_{IV})(1-\epsilon^<em>) + 2\phi c (m_{II} - m_{IV})(1-\epsilon^</em>)}{\phi c \sum_{j=I}^{IV} (m_j(1-\epsilon^<em>) + \epsilon^</em>) + \phi c [(2m_{II} + m_{IV})(1-\epsilon^<em>) + 3\epsilon^</em> + 3V_D]} )</td>
</tr>
</tbody>
</table>
### Table 4.3: Design equations for 3C-ISMB for negligible dead volume and lab scale plant where dead volume and pressure drop along the dead volume has to be accounted for.
At this point it is worth mentioning that although 3C-ISMB and I-SMB are designed in exactly the same manner, i.e. by constraining the four \( m \)-values, the constraint on \( m_{IV} \) has a different physical meaning. Whereas the fulfillment of the \( m_{IV} \)-constraint ensures complete regeneration of the solvent in the case of I-SMB, the same constraint in 3C-ISMB guarantees that the front of component B does not move beyond the outlet of section I. Since Triangle Theory is based on the equilibrium theory model, it is generally understood that a certain safety margin with respect to the boundaries of the complete separation region is required in real systems so as to counter the effects of dispersion \[23\]. Therefore, 3C-ISMB requires generally a slightly larger safety margin on the \( m_{IV} \) boundary due to the different physical meaning of this constraint. As a result the solvent consumption of 3C-ISMB is slightly higher (usually in the order of 5% to 10%) as compared to I-SMB (see chapter \[3\]).

### 4.2.4 Separation performance

The performance of chromatographic separation processes is usually measured in terms of purity, productivity, solvent consumption and recovery. For (modified) SMB processes operated under high purity constraints, i.e. complete separation, the recovery at steady state equals by definition unity, hence only the other three metrics are considered throughout this work.

The purity of the extract (raffinate) \( PU_E \) (\( PU_R \)) is given by

\[
PU_E = \frac{c_{A,E}}{c_{A,E} + c_{B,E}} \quad (4.5a)
\]

\[
PU_R = \frac{c_{B,R}}{c_{A,R} + c_{B,R}} \quad (4.5b)
\]

where \( c_{i,E} \) (\( c_{i,R} \)) is the average concentration of component \( i \) in the extract (raffinate).

The productivity \( PR \) is defined as mass of products per unit time and unit volume of stationary phase, i.e. for 3C-ISMB and I-SMB separations it is given by

\[
PR = \frac{\alpha (Q_{E}c_{A,E} + Q_{R}c_{B,R})}{n_{col}V(1 - \epsilon^*)} \quad (4.6)
\]

where \( Q_E \) and \( Q_R \) stand for the volumetric flow rate of extract and raffinate, \( n_{col} \) for the total number of columns and the step ratio \( \alpha \) (0 < \( \alpha < 1 \)) accounts for the semi-continuous operation of these processes. It is worth mentioning that other definitions of \( PR \) can be found in the literature, however, for chiral separations using the one given above is preferred since it accounts properly for the amount of the expensive stationary phase required for this type of separations.

The specific solvent consumption \( SC \) is usually defined as volume of solvent per mass of products, i.e.

\[
SC = \frac{Q_D + Q_F}{Q_{E}c_{A,E} + Q_{R}c_{B,R}} \quad (4.7)
\]
where $Q_D$ and $Q_F$ are the volumetric desorbent and feed flow rate, respectively. It is noted that the step ratio cancels out, therefore the specific solvent consumption is identical both for SMB and I-SMB as well as for I-SMB and 3C-ISMB assuming identical operating points in terms of $m$-values. The reader is referred to chapter 3 for more details about these performance indices and about the reasons for the enhanced performance of 3C-ISMB.

4.3 Experimental Part

As a proof of concept study, the separation of Tröger’s Base enantiomers on the chiral stationary phase Chiralpak AD in pure ethanol was examined. This system was chosen since its detailed system characteristics are known from previous studies [22, 36, 59]; this makes not only process design easier but it also allows assessing the performance of the new 3C-ISMB technology against other processes. In the following the experimental set-up, the experimental methods, and the materials being used are detailed.

4.3.1 Experimental set-up

The experimental set-up for both the I-SMB and the 3C-ISMB process is based on a modified ÄKTÄ™ explorer 100 system (GE Healthcare Europe GmbH, Freiburg, Germany) [43]. The program controlling all the devices is based on the standard UNICORN™ software (GE Healthcare Europe GmbH, Freiburg, Germany). The experiments were carried out in a 1-1-1-1 (I-SMB), respectively a 1-1-1 (3C-ISMB), closed loop configuration.

The laboratory unit for the 3C-ISMB process was set up according to the flowsheet shown in figure 4.1. The inlet and outlet manifolds 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. Three multi-position valves are connected to the inlet manifolds and to the pumps delivering feed, solvent and recycle stream, respectively. Another three multi-position valves are connected to the outlet manifolds in order to collect the two product streams and to direct the outlet of the recycle stream. A small buffer tank with a volume of approximately 1 ml is used between the recycle outlet and the sucking side of the recycle pump. Direct coupling of recycle outlet to recycle pump resulted in unstable operation, since any air bubble trapped in the recycle lines causes malfunctioning of the recycle pump, hence an installation to remove air bubbles is required. The 1 ml buffer tank is an easy solution to that problem that does not generate too much back mixing.
Figure 4.1: Flowsheet of the experimental 3C-ISMB set-up consisting of four pumps, three chromatographic columns, each equipped with an inlet and an outlet manifold which are connected to six multi-position valves. The small bottle labeled with BT is a small buffer tank with a volume of approximately 1 ml that is used between the recycle outlet and the sucking side of the recycle pump in order to facilitate the removal of trapped air bubbles in the recycle line. It is noted that the conventional I-SMB set-up is easily realized by simply adding a fourth column and consequently adapting the switching procedure.
The I-SMB process was set up analogously by simply adding one module consisting of one chromatographic column as well as an inlet and an outlet manifold which are connected to the switching valves by installing additional tubing. Swapping from I-SMB to 3C-ISMB is accomplished by removing the fourth module from the column train, which can easily be achieved by removing the tubing connecting the outlet of column 4 to the inlet of column 1 and connecting the outlet of column 3 to the inlet of column 1 instead. This purely mechanical alteration of the plant can be carried out in our laboratory in less than five minutes. Additionally, the UNICORN™-code needs to be altered in order to implement a switching regime that accounts for the reduced number of columns.

The extra-column dead volume plays a crucial role in labscale SMB units and consists of three different tubing parts. Namely from the inlet manifold to the column inlet, from the column outlet to the outlet manifold and from the outlet manifold to the inlet manifold of the following column. The volumes of these tubing parts have been determined very precisely using TTBB (1,3,5-tris-tert-butylbenzene) as a tracer. Using these values, the total extra-column dead volume sums up to $V_D = 0.095$ ml. This rather low value could be achieved by using red PEEK tubing (Upchurch Scientific, Oak Harbor, WA, USA) which has inner diameter of only 0.005 in. As a consequence, the pressure drop along the tubing is no longer negligible but has to be accounted for as follows:

\[ \Delta P_{\text{max}} = \phi_c Q_I + (\phi_c + 2\phi_t) Q_{\text{III}} + \phi_c Q_{\text{III}} \]  
\[ \Delta P_{\text{max}} = (f_1\phi_c + f_2\phi_t) Q_{\text{IV}} \]  

where $\Delta P_{\text{max}}$ is the maximum allowable pressure drop, $f_1$ and $f_2$ are process specific constant factors, namely $f_1=4$ ($f_1=3$) and $f_2=3$ ($f_2 = 2$) for I-SMB (3C-ISMB). The constants $\phi_c$ and $\phi_t$ stand for the linear pressure drop coefficient of the column (including manifolds as well as the small pieces of tubing connecting the manifolds to the column) and of the long piece of tubing connecting outlet and inlet manifold, respectively. It is worth noting that for the sake of convenience these constants were based on volumetric flow rates instead of on superficial velocities, as used in the classical form of Darcy’s law. The numeric values of $\phi_c$ and $\phi_t$ are listed in table 4.4. Furthermore, it is noted that the classical pressure drop factor $\phi$ used in the top part of tables 4.2 and 4.3 for units with negligible pressure drop along the dead volume, is obtained by multiplying $\phi_c$ with $A/L$; where $A$ is cross-sectional area and $L$ the length of the column.
### Table 4.4: Operating conditions and separation performance of the experimental I-SMB and 3C-ISMB runs; the position of the operating points in the operating parameter plane are shown in figure 4.9a, respectively in figures 4.3a to 4.8a.

<table>
<thead>
<tr>
<th>Run</th>
<th>(c_F,_{\text{tot}}) [g/l]</th>
<th>Operating mode</th>
<th>Average Flow rate ratio</th>
<th>(t^*) [min]</th>
<th>(\alpha) [-]</th>
<th>Flow rate [ml/min]</th>
<th>Purity [%]</th>
<th>PR [g/l h]</th>
<th>SC [l/g]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>(m_I)</td>
<td>(m_{II})</td>
<td>(m_{III})</td>
<td>(m_{IV})</td>
<td>(Q_I)</td>
<td>(Q_{II})</td>
<td>(Q_{III})</td>
</tr>
<tr>
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<td>5.01</td>
<td>I-SMB opt</td>
<td>5.91</td>
<td>2.05</td>
<td>4.11</td>
<td>1.15</td>
<td>5.56</td>
<td>0.27</td>
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</tr>
<tr>
<td></td>
<td>5.01</td>
<td>3C-ISMB</td>
<td>5.91</td>
<td>2.06</td>
<td>4.12</td>
<td>1.15</td>
<td>5.56</td>
<td>0.27</td>
<td>2.43</td>
</tr>
<tr>
<td></td>
<td>5.01</td>
<td>3C-ISMB opt</td>
<td>5.88</td>
<td>2.05</td>
<td>4.10</td>
<td>1.14</td>
<td>4.28</td>
<td>0.34</td>
<td>2.50</td>
</tr>
<tr>
<td>Run B</td>
<td>5.05</td>
<td>I-SMB opt</td>
<td>5.80</td>
<td>1.84</td>
<td>4.15</td>
<td>1.06</td>
<td>5.14</td>
<td>0.22</td>
<td>3.22</td>
</tr>
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<td>4.14</td>
<td>1.06</td>
<td>5.14</td>
<td>0.22</td>
<td>3.21</td>
</tr>
<tr>
<td></td>
<td>5.05</td>
<td>3C-ISMB opt</td>
<td>5.78</td>
<td>1.83</td>
<td>4.13</td>
<td>1.05</td>
<td>3.87</td>
<td>0.29</td>
<td>3.22</td>
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<td>Run C</td>
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<td>3.79</td>
<td>1.05</td>
<td>5.05</td>
<td>0.21</td>
<td>3.45</td>
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<td></td>
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<td>0.20</td>
<td>3.74</td>
</tr>
<tr>
<td></td>
<td>15.28</td>
<td>3C-ISMB</td>
<td>5.90</td>
<td>1.78</td>
<td>3.72</td>
<td>1.14</td>
<td>5.00</td>
<td>0.20</td>
<td>3.69</td>
</tr>
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<td></td>
<td>15.28</td>
<td>3C-ISMB opt</td>
<td>5.92</td>
<td>1.79</td>
<td>3.73</td>
<td>1.13</td>
<td>3.73</td>
<td>0.27</td>
<td>3.71</td>
</tr>
<tr>
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<td>3C-ISMB opt</td>
<td>5.76</td>
<td>1.65</td>
<td>3.55</td>
<td>1.05</td>
<td>3.71</td>
<td>0.26</td>
<td>3.73</td>
</tr>
<tr>
<td></td>
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<td>3C-ISMB</td>
<td>5.82</td>
<td>2.12</td>
<td>3.07</td>
<td>1.05</td>
<td>3.99</td>
<td>0.26</td>
<td>2.93</td>
</tr>
<tr>
<td></td>
<td>17.37</td>
<td>3C-ISMB opt</td>
<td>5.84</td>
<td>2.38</td>
<td>2.78</td>
<td>1.03</td>
<td>4.15</td>
<td>0.34</td>
<td>2.61</td>
</tr>
</tbody>
</table>
Accounting for the extra-column dead volume according to the method described by Katsuo et al. \cite{22, 58} and taking the pressure drop according to equation (4.8) into account, the design equations given in the lower part of tables 4.2 and 4.3 are obtained and were applied for process design throughout this work.

4.3.2 Experimental methods

In total six experimental runs labelled A to F have been carried out. All experiments were performed under non-linear chromatographic conditions, as total feed concentrations ranging from 5 g/l (run A) to 17.4 g/l (run F) were applied. Each experiment was carried out in three steps, namely the following sequence was applied for runs A to E: (i) start-up in four sections I-SMB mode with optimized conditions, (ii) switch to 3C-ISMB without changing flow rates, switch time and step ratio (non-optimized 3C-ISMB operation) and (iii) 3C-ISMB with optimized operating conditions. The difference between optimized and non-optimized 3C-ISMB operating conditions stems from the fact that switch time and step ratio calculated for I-SMB (tab. 4.2) when applied to 3C-ISMB no longer result in operating substep 2 at $\Delta P_{\text{max}}$, thus the second step of the experimental sequence is suboptimal. Accounting for the reduced pressure drop and applying the equations given in table 4.3 whilst keeping the $m$-values constant, yields optimal 3C-ISMB operating conditions, i.e. operating both substeps at $\Delta P_{\text{max}}$, which is further illustrated by the pressure profile shown in figure 4.2. Run F was also carried out in three steps, however, in this case the plant was always operated in optimized 3C-ISMB mode, but the operating point in the $(m_{II}, m_{III})$-plane was varied.

In all six runs a total number of 28 cycles, the cycle time being defined as $t^* n_{\text{col}}$, was studied and the operating conditions were in each case changed at the end of cycle 12 and 20, respectively. For each cycle the product streams were individually collected in tared flasks and their composition were analyzed offline by HPLC. The feed and desorbent bottles were placed on accurate balances and readings were taken at the end of each cycle. From these readings and the weights of the product flasks the actual volumetric flow rates were calculated assuming a density of 790 g/l, i.e. the density of pure ethanol.

4.3.3 Materials

This work studies the separation of racemic Tröger’s Base (Sigma-Aldrich Chemie GmbH, Buchs, Switzerland) in pure ethanol (analytical grade, Scharlab S.L., Sentmenat, Spain) on Chiralpak AD™ (Chiral Technologies Europe, Illkirch, France). The Chiralpak AD™ stainless steel columns (15 cm × 0.46 cm, 20 µm particle size) were prepacked by the manufacturer and were used for the separation in the I-SMB and 3C-ISMB process unit. For analytical purposes the same stationary phases was used for run A, whereas for runs B to F a Chiralpak IA™ (Chiral Technologies Europe, Illkirch, France) column (25 cm × 0.46 cm, 20 µm particle size) was used. The analytics were carried out on a Dionex Ultimate 3000 HPLC unit (Sunnyvale, CA, USA) using also pure ethanol as mobile phase.
Figure 4.2: Pressure versus cycle number during run B: The dashed lines indicate a changes of the operating mode, namely the unit was operated from cycle 1 to 12 in optimized I-SMB mode, from cycle 13 to 20 in 3C-ISMB mode without changing flow rates and switch time and from cycle 21 to 28 in optimized 3C-ISMB, i.e. at the maximum allowable pressure drop.
The overall void fraction, $\epsilon^*$, of the preparative columns was determined by injecting 1,3,5-tris-tert-butylbenzene (Sigma-Aldrich Chemie GmbH, Buchs, Switzerland), which is considered to be non-retained, according to the following equation

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

where $V$ is the column volume, $Q$ is the applied flow rate and $t_0$ is the residence time of a non-retained species.

**4.4 Results and Discussion**

The results of all six experimental runs A to F are presented in terms of outlet stream concentrations and purities in figures 4.3 to 4.8. In each case the position of the three operating points in the $(m_{II}, m_{III})$-plane is shown in sub figure (a). Note that the small deviations in the position of the operating point within one run are due to the fact that these points were determined from the actual flow rates in the unit (see section 4.3). For runs A to E it was actually aimed at identical $m$-values for all three operating modes, however exact matching is difficult due to some variation of the actual flow rates from the desired set point. The operating points and their corresponding performance in terms of productivity and solvent consumption are furthermore summarized in figure 4.9 and table 4.4.

First of all it is worth commenting on the general trends observed in runs A to E; run F will be discussed separately due to the different experimental procedure applied in this run. With reference to figures 4.3b to 4.7b representing the product stream concentrations of runs A to E it is noted that cyclic steady state is essentially reached after four cycles. After having attained cyclic steady state the unit is operated for another eight cycles in conventional four columns I-SMB mode so as to demonstrate the stable steady state behavior which is well reflected in figures 4.3b to 4.7b. When the fourth column is removed and the unit is started to be operated in the novel 3C-ISMB mode from cycle 13 onwards, the concentrations of the raffinate stream initially drop to a lower value. This behavior is expected since the column that had been used to adsorb the weakly retained component B immediately before changing the operating mode is now disconnected from the column train. Moreover, the small buffer tank between the recycle outlet and the sucking side of the recycle pump (see figure 4.1) undergoes a transient phase during which its content is enriched in component B. Therefore, it requires three to four cycles in the new operating mode during which the concentrations of the raffinate stream steadily increase until a new cyclic steady state is attained. In the new cyclic steady state, the raffinate stream concentrations are identical to the initial steady state concentrations and furthermore remain constant when switching from non-optimized 3C-ISMB to optimized 3C-ISMB mode. The new steady state is generally reached from cycle 17 and remains stable until the end of each experiments, i.e. until cycle 28. Run D (see figure 4.6b) marks an exception where an unexpected overshoot in cycle 16 is observed which cannot
Figure 4.3: Results of run A: (a) Purities of the product streams versus the cycle number and operating points in the $(m_{II}, m_{III})$-plane. (b) Concentrations in the product streams raffinate (solid lines) and extract (dashed lines) versus the cycle number, the lines without marker represent the concentrations of the polluting species, i.e. component A (B) in the case of the raffinate (extract). In both figures, the dashed vertical lines indicate a change in the operating conditions, namely optimized I-SMB (shown as $\bigcirc$ in the operating parameter plane) from the begin until cycle 12, non-optimized 3C-ISMB (□) from cycle 13 to 20 and optimized 3C-ISMB (⋄) from cycle 21 to 28.
Figure 4.4: Results of run B: (a) Purities of the product streams versus the cycle number and operating points in the \((m_{II}, m_{III})\)-plane. (b) Concentrations in the product streams raffinate (solid lines) and extract (dashed lines) versus the cycle number. The same notation as in figure 4.3 applies.
Figure 4.5: Results of run C: (a) Purities of the product streams versus the cycle number and operating points in the \((m_{II}, m_{III})\)-plane. (b) Concentrations in the product streams raffinate (solid lines) and extract (dashed lines) versus the cycle number. The same notation as in figure 4.3 applies.
Figure 4.6: Results of run D: (a) Purities of the product streams versus the cycle number and operating points in the \((m_{\text{II}}, m_{\text{III}})\)-plane. (b) Concentrations in the product streams raffinate (solid lines) and extract (dashed lines) versus the cycle number. The same notation as in figure 4.3 applies.
Figure 4.7: Results of run E: (a) Purities of the product streams versus the cycle number and operating points in the \((m_{\text{II}}, m_{\text{III}})\)-plane. (b) Concentrations in the product streams raffinate (solid lines) and extract (dashed lines) versus the cycle number. The same notation as in figure 4.3 applies.
Figure 4.8: Results of run F: (a) Purities of the product streams versus the cycle number and operating points in the \((m_{II}, m_{III})\)-plane. (b) Concentrations in the product streams raffinate (solid lines) and extract (dashed lines) versus the cycle number. In both figures, the dashed vertical lines indicate a change in the operating conditions, though the unit is always run in optimized 3C-ISMB mode, decreasing feed flow rates are studied, i.e. the operating point is stepwise moved from \(\bigcirc\) (cycle 1 to 12) towards operating \(\bigdiamond\) (cycle 21 to 28). Besides that, the same notation as in figure 4.3 applies.
be explained and is most likely an artifact; however, also in this run the new steady state is eventually reached by cycle 20. Moreover, it is noted that the new steady state concentrations are also in this case consistent with the initial ones. As far as extract stream concentrations are concerned, it is noted that the steady state values attained after four cycles remain essentially constant over the whole duration of the experiments, no matter what the operating mode is. Such a behavior is expected since the extract withdrawal is essentially not affected by the implementation of the 3C-ISMB operating mode.

With reference to figures 4.3a to 4.7a it is worth pointing out that the purity is generally very high and - most importantly - not affected by changing from the four-column I-SMB to the three-column 3C-ISMB process. This is a very important result as it clearly demonstrates that the reduction of the number of columns is not penalizing in terms of purity, but it enables an enhancement of productivity by as much as 82% as illustrated in figure 4.9b, i.e. the novel process allows for significant performance gains without any drawback.

Having made this general statement about the purities, it is worth discussing each run individually so as to point out some particularities and to substantiate the claim of achieving identical purity, no matter whether four or three columns are being used. In run A (see figure 4.3) the operating points of all three modes of operation are essentially the same, lie within the region of complete separation according to Triangle Theory and have a small safety margin from both boundaries of the triangle. Consequently, the purities of both the raffinate (99.9%) and the extract (>99.5%) are very high and constant during the whole experiment.

In run B (see figure 4.4) almost the same total feed concentration as in run A is studied and the operating points are still within the region of complete separation, however, with a smaller safety margin from the impure extract region. Moreover, the third operating point, i.e. the one representing the optimized 3C-ISMB mode, is slightly more to the left than the first two operating point which is due to the difficulty of perfectly matching the desired set-point. Compared to run A the same raffinate purities of 99.9% are obtained, however, the reduced safety margin from the impure extract region is reflected by a slightly worse extract purity, namely 98.9% and 99.0% for the first two operating points and 98.6% for the third one which is well in agreement with its position slightly to the left of the other two operating points.

In run C (see figure 4.5) the feed concentration is doubled with respect to runs A and B, furthermore all the operating points lie in the impure extract region and somewhat vary between each mode of operation. Consequently, also in this case the raffinate purity is >99.9% for all three operating points, but the extract purity is obviously worse than in the previous runs, namely 97.8%, 98.1% and 97.6% for I-SMB, non-optimized 3C-ISMB and optimized 3C-ISMB, respectively. These slightly varying extract purities can be explained by the position of the operating point in the \((m_{II}, m_{III})\)-plane; when switching from I-SMB (circle in the operating parameter plane of figure 4.5a) the operating point moves slightly to the right and thus the purity in non-optimized 3C-ISMB (represented by the square) is
Figure 4.9: Summary of all experimental runs: (a) Operating points in the operating parameter planes. (b) Productivity of runs A-E. The dashed vertical lines indicate a change in the operating conditions, i.e., they represent a change from optimized I-SMB (cycles 1-12) to non-optimized 3C-ISMB (cycles 13-20) and optimized 3C-ISMB (cycles 20-28). (c) Productivity vs. total feed concentrations for runs A-F and the three modes of operation. (Note: In Run E, cycle 26 the weighted mass of the collected product streams is erroneous due to a spill of product solution. Therefore the corresponding point is represented as filled diamond and not taken into account for drawing the connecting line.)
slightly higher, whereas the switch from non-optimized 3C-ISMB to optimized 3C-ISMB (represented by the diamond) is accompanied by a shift of the operating point to the left and thus a drop in purity.

Runs D and E (see figures 4.6 and 4.7) are carried out using almost the same feed concentration and operating points within the region of complete separation, however, using a very small safety margin to the impure extract region in run D, and to the impure raffinate region in run E. As a consequence, the extract purity increases from 99.0% in run D to roughly 99.5% in run E, whereas the raffinate purities are >99.9% in both run D and E. Therefore the raffinate purity appears to be less prone to drops caused by operation close to the impure raffinate region. Moreover, it is noted that no significant differences in the purity due to the change of the operating mode can be observed.

In run F (see figure 4.8) the plant is operated during the whole experiment in optimized 3C-ISMB mode, however, three different operating points in the \((m_{II}, m_{III})\)-plane are studied. Starting from the tip of the triangle, the operating point moves stepwise closer to the diagonal as the feed flow rate is decreased. As expected, the first operating point yields an extract purity of 98.2%. When moving closer to the diagonal, the purity increases to 99.6%, whereas a further reduction of the feed flow rate does no longer result in better extract purity. As far as raffinate purity is concerned, no significant difference between the three operating points can be observed. Moreover, it is noted that the start-up period, i.e. the time until cyclic steady state is attained, is significantly longer as compared to runs A to E which is a consequence of the small buffer tank between the recycle outlet and the sucking side of the recycle pump (see figure 4.1). As mentioned in section 4.3.1 this tank of approximately 1 ml is necessary to guarantee stable operation of the recycle pump. However, it leads to prolonging the start-up phase since it is initially filled with pure solvent and undergoes a transient phase as mentioned above. In other words, the same effect causing a drop in average raffinate concentration when switching from I-SMB to 3C-ISMB in runs A to E, causes a prolonged start-up phase for 3C-ISMB with respect to I-SMB where the transient is not relevant since the recycle consists of pure solvent.

The series of experiments in run F gives evidence that the experimentally achievable extract purity is slightly lower than the corresponding raffinate purity, i.e. an upper limit in extract purity of about 99.5% cannot be overcome by changing the operating point. This asymmetry in the experimentally achievable purities can also be observed in runs A to E for both 3C-ISMB and I-SMB, as well as for I-SMB and SMB in previous studies [22, 36]. Therefore, one can conclude that this limitation is not specific to the new 3C-ISMB process, but it is more general and might be related to a set-up specific unidentified cause, e.g. some sort of very mild cross-contamination. It is worth noting that the identification of the cause of this contamination of the extract is made very difficult indeed by the fact that it is a very mild contamination. It is also important to mention that when 99.5% is considered to be the specification for extract purity, then the relative performance of the different operating points in the \((m_{II}, m_{III})\)-plane is consistent with their relative position and with Triangle Theory. In fact this value is not achieved in runs B, C, and D only, whose operating point is either outside the triangle or very close to its
left boundary. This result provides therefore evidence that 3C-ISMB design through this short-cut method does not only work theoretically as demonstrated in chapter 3, but also experimentally.

4.5 Conclusions

After having successfully demonstrated the superior performance of 3C-ISMB with respect to I-SMB through detailed simulations in chapter 3, this chapter examined the same system and processes experimentally. In a comprehensive set of six experimental runs, each studying three different operating conditions, the main conclusions drawn from the theoretical analysis were confirmed. Namely, the novel three-column intermittent simulated moving bed (3C-ISMB) process outperforms I-SMB substantially (up to 82% in terms of productivity) and the design through Triangle Theory is applicable, which is an important advantage compared to other modified SMB schemes. Moreover, this work demonstrated that the practical implementation of this new mode of operation is rather easy.

As to the comparison with other processes, especially conventional SMB, it is worth pointing out that Katsuo et al. reported previously on the experimental comparison of I-SMB and SMB studying the same system and feed concentrations [36], thus demonstrating that I-SMB outperforms SMB by roughly a factor two in terms of productivity. Since the present work has now yielded an additional factor of up to 1.8 between 3C-ISMB and I-SMB, one can conclude that 3C-ISMB outperforms conventional SMB in 1-2-2-1 configuration by at least a factor three. However, it is worth mentioning that although the relative performance of SMB and I-SMB given in [36] can be compared to the relative performance of I-SMB and 3C-ISMB reported here, a direct comparison of the absolute productivity values calculated in the previous work [36] and this work is not possible. A fair experimental comparison of different processes requires in fact that the experiments are run under exactly the same conditions, which is not the case since a modified experimental set-up was used in this work; namely a new batch of chromatographic columns and new tubing having a larger pressure drop factor has been used. Therefore, the volumetric flow rates and thus the productivities for I-SMB reported in [36] are slightly higher than those reported here.

As an outlook, it is worth pointing on an other issue; chromatographic separation of binary mixtures by SMB and modifications thereof are considered to be well understood and research activities in this area are diminishing. The focus has, however, shifted towards three-fraction separations since real mixtures of isomers or enantiomers often contain not only the two main species but also one or more impurities. Ideally, such separation problems should be solved in a single unit operation capable of three-fraction separation. Many good ideas and concepts to solve this task have emerged, however, in terms of productivity most of them are not convincing. A recent theoretical study has, however, demonstrated that the concept of a SMB cascade is promising since it outperformed both the integrated 8-zone SMB as well as the JO process [65]. Although another study [66]...
came to a somehow different conclusion, I believe that the SMB cascade is not only promising in terms of productivity, but also has a couple of practical advantages; namely, the possibility of using different column dimensions in the two stages, or of distributing the pressure drop over the two independent stages. However, cascades of two standard SMB units would require at least 8 columns, more realistically even more since it is well known that a conventional SMB in 1-1-1-1 configuration suffers from low purity \cite{22}. Therefore, the SMB cascade seems relatively expensive in terms of equipment costs. In contrast, the implementation of a 3C-ISMB cascade would require only 6 columns, i.e. the same number of columns normally used in standard SMB for binary separations. Thus the challenging task of three-fraction separation could be solved efficiently with the same volume of stationary phase, which is nowadays being used for simple binary separations. The next chapter will, therefore, examine the performance of a 3C-ISMB cascade for three fraction separation.

4.6 Nomenclature

- $A$: Column cross section area [cm$^2$]
- $a_v$: Specific surface of the adsorbent particles [cm$^{-1}$]
- $a_{i,1}$, $a_{i,2}$: Parameters in Bi-Langmuir isotherm [-]
- $b_{i,1}$, $b_{i,2}$: Parameters in Bi-Langmuir isotherm [l g$^{-1}$]
- $c_{e,i}$: Concentration of component $i$ in external stream $e$ [g l$^{-1}$]
- $c_{F,tot}$: Total feed concentration [g l$^{-1}$]
- $c_i$: Concentration of component $i$ [g l$^{-1}$]
- $D_{ax,i}$: Axial dispersion coefficients of component $i$ [cm$^2$ s$^{-1}$]
- $\Delta P$: Pressure drop [bar]
- $\Delta P_{\text{max}}$: Maximum allowable pressure drop [bar]
- $f_1$, $f_2$: Process specific constants [-]
- $H_i$: Henry’s constant of component $i$ [-]
- $k_{s,i}$: Mass transfer coefficient of component $i$ [s$^{-1}$]
- $L$: Column length [cm]
- $m_j$: Dimensionless flow rate ratio in section $j$ [-]
- $n_{\text{col}}$: Total number of columns [-]
- $n_j$: Number of columns in section $j$ [-]
- $PR$: Productivity [g l$^{-1}$ h$^{-1}$]
- $PU_e$: Purity of external stream $e$ [%]
- $Q$: Volumetric flow rate [ml min$^{-1}$]
- $Q_e$: Volumetric flow rate of external stream $e$ [ml min$^{-1}$]
- $Q_j$: Volumetric flow rate in section $j$ [ml min$^{-1}$]
- $Q_{\bar{j}}$: Average volumetric flow rate in section $j$ [ml min$^{-1}$]
- $q_i$: Adsorbed phase concentration [g l$^{-1}$]
- $SC$: Solvent consumption [l g$^{-1}$]
- $t_{R,i}$: Retention time of component $i$ [min]
Residence time of an unretained component $i$ [min]

Switching time [min]

Superficial velocity [cm min$^{-1}$]

Column volume [ml]

Total extra-column dead volume per section [ml]

Greek Letters

$\alpha$  Step ratio ($0 \leq \alpha \leq 1$) [-]

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

$\epsilon_b$  Bed void fraction [-]

$\nu$  Phase ratio [-]

$\phi$  Pressure drop factor in Darcy’s law [bar min cm$^{-2}$]

$\phi_c$  Pressure drop factor of a column [bar ml$^{-1}$]

$\phi_t$  Pressure drop factor of the tubing connecting two columns [bar ml$^{-1}$]

Subscripts and Superscripts

A  Weak retained component

B  Strong retained component

D  Desorbent

E  Extract

$e$  Index for external stream ($e$=D,E,F,R)

F  Feed

$i$  Component index ($i$=A,B)

$j$  Section index ($j$=I,II,III,IV)

max  Maximum allowable

R  Raffinate
Three column intermittent simulated moving bed chromatography: Cascade operation for center-cut separations

5.1 Introduction

Three column intermittent simulated moving bed (3C-ISMB) chromatography has been introduced and theoretically studied in chapter 3. Chapter 4 further demonstrated its potential for binary separations experimentally. This new type of multi-column chromatographic process can be regarded as a modification of the commercialized intermittent simulated moving bed (I-SMB) process [35] or more generally of classical simulated moving bed (SMB) chromatography [5, 9].

SMB is a well-established binary separation process being applied at widely varying scales and in different fields of applications that range from the petrochemical [8] and the sugar [18] industry to the fine chemicals and pharmaceutical industry [5]. In the latter area the technology is mainly used for separating enantiomers [5], which not only requires expensive chiral stationary phases (CSPs) but also frequently involves more than two compounds due to the presence of either several stereocenters or of impurities stemming from upstream processes. Both aspects make this kind of separation rather challenging.
and have triggered two different research interests aiming at (i) the enhancement of productivity for binary separations and thus a more effective use of the stationary phase \[24, 25, 26, 27, 28, 30, 35, 67\], and (ii) the extension of the SMB technology to enable three fraction separations \[37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 50, 55, 65, 66, 68\]. The former objective has been the subject of chapters 3 and 4, whereas the present chapter exploits those results so as to address the latter. Therefore, the main conclusions of our previous work on the 3C-ISMB technology will be briefly summarized in section 5.3.1, whereas the remaining part of this section is focused on the challenges associated with the chromatographic purification of chiral substances involving more than two components, especially compounds with more than one stereocenter, where the target component is neither the most nor the least retained one.

Most of the earlier studies on three-fraction separations cited above are focused on the process itself and are limited to theoretical process assessment under linear chromatographic conditions. However, the feed concentration is a critical parameter determining productivity and thus economic viability of any chromatographic separation process \[23\]. Therefore, there is a need for a more holistic approach considering also high feed concentrations, i.e. non-linear chromatographic conditions, which requires a more rigorous evaluation of the system characteristics, especially of the adsorption isotherm. The latter is made particularly difficult for chiral substances involving several stereocenters due to not only the number of components competing for the same adsorption sites, but also due to the fact that the pure single components are usually not available.

In this chapter these issues are addressed by proposing a general design methodology that consists of comprehensive guidelines ranging from the identification of the chromatographic system, i.e. a proper combination of stationary and mobile phase, over the process design for non-linear chromatographic conditions, to the realization of the preparative isolation of an intermediate retained target stereoisomer. This methodology will be validated experimentally by studying the purification of an intermediate retained stereoisomer of Nadolol in Heptane/Ethanol/DEA on Chiralpak AD. Nadolol is a chiral API with three stereogenic centers, two of them being locked in cis-configuration, i.e. it consists of four stereoisomers. To the best of our knowledge this is the first experimental study on the SMB separation of an intermediate eluting stereoisomer under non-linear chromatographic conditions.

The preparative separation will be carried out using a 3C-ISMB cascade, therefore the above mentioned methodology is tailored to this novel process type. However, it is worth mentioning that the same approach is applicable for the SMB cascade \[37, 38\] and partly for other SMB based ternary separation processes proposed earlier \[37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 50, 55, 65, 66, 68\], as it will become clearer when discussing our general solution strategy.
5.2 Design Methodology

The design methodology proposed in this work is illustrated in figure 5.1 and will be explained in the following for a generic quaternary mixture of four stereoisomers that are labelled A, B, C, and P where P represents the intermediately retained target component, whereas A and C denote the least and most retained component, respectively, and B can elute either before or after the target component P. In order to be consistent with the following experimental part (sections 5.4 and 5.5), it is here assumed that the order of retention is given by A-B-P-C.

The selection of the proper combination of CSP and mobile phase (MP) is the starting point of any chromatographic separation process. Given the wealth of commercially available CSPs [69] and the possible combinations thereof with MPs, this first step is anything but trivial. Generally, it requires an extensive and cumbersome screening involving several CSPs and applying different MPs. Guidelines for an efficient screening are available from column manufacturers such as Chiral Technologies and will not be treated here. This step might be further assisted through consulting the relevant open literature or the application guides from column suppliers. In any case, this first step is completed once a combination of CSP and MP is found, that successfully resolves at least components B, P, and C.

In the next step, the retention behavior of the four components under linear conditions for different solvent compositions is studied. It is noted that this step is restricted to the solvent mixture selected in the previous step, i.e. only the ratio of polar and apolar solvent is varied so as to find a good compromise between retention and resolution. More specifically, the MP composition should be chosen such as to obtain Henry’s constants in the range between 1 and 5, which as a rule of thumb is a good working range for preparative separations [70]. This step is assisted by applying the Soczewinski equation [71] which relates Henry’s constants to solvent composition as further explained in section 5.5.1.

Upon completion of step 2 the separation sequence needs to be determined, as for cascades of distillation columns [72]. In other words, it is necessary to decide whether stages 1 and 2 are coupled via the extract (split AB/PC in stage 1) or the raffinate (split ABP/C in stage 1) stream of the first stage. It is proposed to base this decision on the knowledge of the linear adsorption behavior as described in section 5.3.3 where a set of heuristics for determining the optimal separation sequence is developed.

Next, the MP composition is fixed based on the previous characterisation and the non-linear adsorption characteristics are determined by first performing a small number of frontal analysis (FA) experiments [60] and then fitting a multi-component competitive Langmuir adsorption isotherm. This method is relatively time-consuming as it requires fraction collection and offline analysis of the collected fractions due to the fact that no single components are available. It is worth pointing out, that the adsorption characteristics of such a four component system can be relatively complex, i.e. it is usually difficult to accurately describe all effects observed in the FA experiments. However, it is proposed to fit a relatively simple adsorption isotherm model to the experimental data, even if
Determination of competitive adsorption isotherm
Determination of separation sequence
Design of stage $s$ by Triangle Theory
Run preparative separation of stage $s$

Figure 5.1: Overview on the general design methodology proposes in this work ($s$ represents the stage number).
CHAPTER 5. 3C-ISMB: CASCADE OPERATION

A more complex behavior of the four component system would require a more complex isotherm. This approach is justified and fit for the targeted purpose, i.e. the design of 3C-ISMB separations, as long as the simple model is able to capture the relevant composition fronts accurately (section 5.5.2). It is further noted that this simplified approach might require to repeat this step for the ternary (raffinate coupling) or binary (extract coupling) mixture representing the feed stream to stage 2, as it will be discussed later in this section as well as in section 5.5.3.

In the following step the 3C-ISMB separation of the first stage \( s = 1 \) is designed by applying the well-known Triangle Theory [23]. The applicability of this method for binary 3C-ISMB separations has been demonstrated in chapters 3 and 4, which is an important advantage to other advanced SMB processes as it simplifies the process design considerably. Moreover, it is noted that the use of a multi-component competitive Langmuir isotherm allows for applying the corresponding version of Triangle Theory derived earlier [73], i.e. simplifying the adsorption characteristics is not only easing the previous step but also the actual design of the 3C-ISMB operation. More details on the design of the individual stages are given in section 5.3.2.

Afterwards, the first stage separation is carried using the operating parameters derived from Triangle Theory which yields the intermediate product, i.e. a mixture consisting of \( A, B, \) and \( P \) (\( P \) and \( C \)) in the case of raffinate (extract) coupling. This intermediate product should be as pure as possible with respect to the heavy (light) impurity \( C \) (\( A \) and \( B \)) since any amount of this impurity carried over to stage 2 would end up in the final product.

As far as the design of the second stage is concerned, the cascade operation offers much more flexibility as compared to alternative, fully integrated, process schemes. In particular, one can use different column dimensions and/or a different solvent composition in the second stage. Both options can be exploited to enhance the productivity of the overall cascade and are represented in figure 5.1 with the boxes "Re-scaling of second stage" and "Choice of MP composition", respectively. The former accounts for the fact that the raffinate (extract) flow rate of stage 1 must be equal to the feed flow rate of stage 2; re-scaling stage 2 accordingly allows for running both stages under optimal conditions with respect to switching times and step ratios (see section 5.3.2). The latter refers to the fact that the best solvent composition for stage 1 might not necessarily be the best composition for stage 2. For the sake of illustration, let us consider a case where component \( C \) is much more retained than the other three. In this scenario, the raffinate coupling scheme would be applied and a solvent composition that yields a reasonable low value for the Henry’s constant of component \( C \) would be selected for stage 1. However, the corresponding MP composition would most likely not resolve well the other three components, which does not matter for stage 1 but becomes problematic for stage 2. Therefore, it is worth considering tuning the MP between the two stages. This should not involve a complete solvent exchange, which would hamper continuous operation of the cascade. However, simple changes, such as diluting the intermediate product with apolar (polar) fresh solvent are possible in a continuous manner and increase the Henry’s constants in normal (reversed)
phase chromatography and thus potentially also resolution. As a result, this approach can be beneficial regarding the performance of the overall cascade as shown in section 5.5.4.

It is evident that the adsorption isotherm for the mixture representing the feed to the stage 2 needs to be redetermined in case the MP of stage 2 is different than the one used in stage 1. However, the same might be required for cases where the MP composition is not changed between the two stages, which is a consequence of the simplified isotherm model. More specifically, the Langmuir model fitted to the initial mixture might not describe the relevant composition fronts of the intermediate product accurately enough, if the removed components, i.e. C for raffinate coupling or A and B for extract coupling, competed with the remaining components, i.e. A, B, and P for raffinate coupling or P and C for extract coupling, in a more complex manner. Therefore, these cases require a redetermination of the isotherm of the intermediate product using the same approach outlined above for the initial mixture.

Once the isotherm parameters for stage 2 are determined, the second stage is designed similarly to stage 1, the column dimensions are re-scaled and the separation is carried out so as to recover the final product P in the extract (raffinate) stream of stage 2 in the case of raffinate (extract) coupling.

5.3 The 3C-ISMB cascade

The 3C-ISMB process as being described in chapters 3 and 4 is characterized by (i) intermittent feed and product withdrawal and (ii) use of three sections, each consisting typically of only one chromatographic column. The intermittent feed and withdrawal follows from the division of the switching period into substeps; in substep 1 the 3C-ISMB process is operated identically to a standard 3-zone SMB process, whereas in substep 2 all inlet and outlet ports are closed and the fluid is just circulated through the column train. Although the same basic principle is applied in the I-SMB process [30, 35], substep 2 of 3C-ISMB is fundamentally different due to the lack of a fourth section. As a result a stream containing the weakly retained component is directly recycled from section III to section I, i.e. 3C-ISMB does no longer perform a full regeneration of stationary and mobile phases. Therefore, the stationary phase is more efficiently used and additionally higher volumetric flow rates are possible thanks to a reduction of the overall pressured drop along the unit. Chapter 3 demonstrated that this new mode of operation allows for significant improvements of productivity with respect to I-SMB, which itself was previously shown to outperform standard SMB [22, 36].

The 3C-ISMB cascade can be realized by coupling two 3C-ISMB units via either the raffinate or the extract stream of the first unit, or stage. A detailed description of the 3C-ISMB process and the design methods can be found in chapter 3. The methodology derived there can be directly applied to each of the individual stages and will not be discussed again here. For the sake of brevity this section is restricted to a description of the overall process followed by a theoretical study on the preferred order of separation.
5.3.1 Process Description

Figure 5.2 shows a general and schematic process flow diagram (PFD) of a 3C-ISMB cascade. It consists of two 3C-ISMB stages each performing a binary split of the components fed via the input stream. For the sake of illustration the discussion in this section is simplified to a ternary separation problem, which e.g. represents a quaternary mixture as mentioned in section 5.2 where components A and B co-elute. Thus, in the following only components A, P, and C are considered, and it is noted that A and C can also represent pseudo components that stand collectively for the light and heavy impurities, respectively. Depending on the coupling strategy, the intermediate product that is the feed stream to stage 2 consists of either P+C (extract coupling) or A+P (raffinate coupling). As a result, the final product is collected from the raffinate (extract) port of stage 2 in the case of extract (raffinate) coupling. The streams labeled as waste 1 and waste 2 represent the outlet streams that do not contain the target component, i.e. it depends on the nature of the feed mixture whether these streams are indeed waste or contain...
other valuable products. Finally, it worth commenting on the buffer tank between stages 1 and 2 which is needed if the two stages were operated with different switching times and/or different step ratios. Under these conditions one stage might be in the productive substep 1, whilst the other one is in recycling mode, i.e. substep 2. These differences are easily buffered by using the design shown in figure 5.2. In other words, the buffer tank enables to operate both semi-continuous stages under optimal operating conditions, i.e. it eventually provides two additional degrees of freedom at negligible expenses.

5.3.2 Process Design

The individual stages can easily be designed by Triangle Theory [23] as demonstrated in chapters 3 and 4 using the following definition of the dimensionless flow rate ratios

\[ m_{j,s} = \frac{\hat{Q}_{j,s} t^*_s - V_s \epsilon^*_s}{V_s (1 - \epsilon^*_s)} \quad (s = 1, 2) \]  

(5.1)

where \( m_{j,s} \) is the dimensionless flow rate ratio in section \( j \) of stage \( s \), \( \hat{Q}_{j,s} \) is the average volumetric flow rate in section \( j \) of stage \( s \), \( t^*_s \) is the switch time of stage \( s \), \( V_s \) is the column volume of stage \( s \) and \( \epsilon^*_s \) the overall void fraction of stage \( s \). The average volumetric flow rates are defined as

\[ \hat{Q}_{j,s} = \alpha_s Q_{j,s} + (1 - \alpha_s) Q_{IV,s} \quad (j = I, II, III) \]  

(5.2a)

\[ \hat{Q}_{IV,s} = (1 - \alpha_s) Q_{IV,s} \]  

(5.2b)

where \( \alpha_s \) is the step ratio of stage \( s \), which can take values ranging from zero to one. Finally the optimal switching time \( t^*_s \) and step ratio \( \alpha_s \) are obtained by enforcing the condition that the pressure drop through the set of columns is always equal to its maximum permitted value, \( \Delta P_{\text{max},s} \), hence one gets:

\[ t^*_s = \frac{\phi_s L_s^2}{\Delta P_{\text{max},s}} \sum_{j=I}^{III} n_{j,s} (m_{j,s} (1 - \epsilon^*_s) + \epsilon^*_s) \]  

(5.3a)

\[ \alpha_s = \frac{\sum_{j=I}^{III} n_{j,s} (m_{j,s} - m_{IV,s})(1 - \epsilon^*_s)}{\sum_{j=I}^{III} n_{j,s} (m_{j,s} (1 - \epsilon^*_s) + \epsilon^*_s)} \]  

(5.3b)

where \( n_{j,s} \) is the number of columns in section \( j \) of stage \( s \), \( \phi_s \) is the pressure drop factor in Darcy’s law for stage \( s \) and \( L_s \) is the column length in stage \( s \). Assuming that both stages have equal column dimensions and designing each stage according to equations (5.1) to (5.3), ensures that both stages are operated under optimal conditions with respect to flow rates, switching time and step ratios. However, continuous operation would not be feasible since on the one hand switching times and step ratios of the two stages are generally not equal; on the other hand, the average flow rate of the intermediate product is generally larger than the average feed flow rate that could
be processed in such a second stage. The former hurdle to continuous operation is easily overcome by coupling the two stages via a buffer tank. The latter is addressed by scaling the column volume of the second stage according to

$$V_2 = rV_1$$  \hspace{1cm} (5.4)

where \(r\) is a linear re-scaling factor. The re-scaling is carried out over the column diameter so as to keep the pressure drop constant and has to fulfill the following conditions:

$$r_{\text{case1}} = \frac{Q_{1.1} - Q_{2.1}}{Q_{3.2}^* - Q_{2.2}^*} = \frac{t_1^*(m_{1.1} - m_{2.1})}{t_1^*(m_{3.2} - m_{2.2})}$$ \hspace{1cm} (5.5a)

$$r_{\text{case2}} = \frac{Q_{3.1} - Q_{4.1}}{Q_{3.2}^* - Q_{2.2}^*} = \frac{t_2^*(m_{3.1} - m_{4.1})}{t_1^*(m_{3.2} - m_{2.2})}$$ \hspace{1cm} (5.5b)

where \(r_{\text{case1}}\) (\(r_{\text{case2}}\)) is the dimensionless re-scaling for the extract (raffinate) coupling and \((Q_{3.2}^* - Q_{2.2}^*)\) denotes the average feed flow rate to an unscaled second stage, i.e. a hypothetical second stage that has the same column dimensions as stage 1. For the sake of clarification, it is noted that \(m\)-values, switching time, and step ratio of scaled and unscaled stage 2 are identical; only the flow rates differ as underlined by using primed variables for the flow rates of an unscaled stage 2 in Equation (5.5) and later. Equation (5.5) ensures that the average feed flow rate of stage 2 matches the average flow rate of the intermediate product. This guarantees that the filling level of the buffer tank attains a cyclic steady state which is a necessary requirement in a continuous production environment.

These re-scaling factors play an important role in the separation performance of a cascade as discussed in the next section.

### 5.3.3 Separation performance and order of separation

For complete separation, the productivity of an individual stage \(s\), \(PR_s\), is most conveniently defined as amount of target component fed per unit time and unit volume of stationary phase, i.e.

$$PR_s = \frac{\dot{Q}_{F,s}c_{P,F,s}}{n_{\text{tot},s}V_s} = \frac{(m_{3,s} - m_{2,s})(1 - \epsilon_s^*)c_{P,F,s}}{n_{\text{tot},s}t_s^*}$$ \hspace{1cm} (5.6)

where \(\dot{Q}_{F,s}\) is the average feed flow rate to stage \(s\), \(c_{P,F,s}\) the feed concentration of target component \(P\) for stage \(s\), and \(n_{\text{tot},s}\) the total number of columns of stage \(s\). Making use of the re-scaling factor \(r\), the overall cascade productivity, \(PR\), is similarly defined as:

$$PR = \frac{\dot{Q}_{F,1}c_{P,F,1}}{(n_{\text{tot},1} + n_{\text{tot},2}r)V_1} = \frac{(m_{3,1} - m_{2,1})(1 - \epsilon_1^*)c_{P,F,1}}{(n_{\text{tot},1} + n_{\text{tot},2}r)t_1^*}$$ \hspace{1cm} (5.7)
The second important separation performance metric is the specific solvent consumption which stands for the amount of solvent needed to separate a certain amount of input material. Therefore, the specific solvent consumption, \( SC_s \), of stage \( s \) is given by

\[
SC_s = \frac{\hat{Q}_{D,s} + \hat{Q}_{F,s}}{Q_{F_c}^{P,F,s}} = \frac{1}{c_{P,F,s}} \left( 1 + \frac{m_{1,s} - m_{4,s}}{m_{3,s} - m_{2,s}} \right)
\]

(5.8)

where \( \hat{Q}_{D,s} \) is the average volumetric fresh solvent flow rate. The specific solvent consumption of the entire cascade is finally given by

\[
SC = \frac{\hat{Q}_{D,1} + r\hat{Q}_{D,2} + \hat{Q}_{F,1}}{Q_{F_c}^{P,F,s}}
\]

(5.9)

where \( \hat{Q}_{D,2} \) refers to the average desorbent flow rate of the unscaled second stage.

With the separation performance metrics defined in equations (5.6) to (5.9), the optimal separation sequence can now be addressed. A well-known heuristic from distillation cascades says that the easy separation should be always performed first [72], as also postulated by Nowak et al. for SMB cascades. However, since the volumetric flow rate of the extract stream is usually larger than that of the raffinate, the second unit might have to process a larger and more diluted intermediate product stream if the extract coupling scheme is chosen, i.e. the second unit gets larger thus compromising productivity. Moreover, the extract coupling requires a higher solvent consumption in the second stage since the most retained component is still present in the intermediate product. Therefore, it is worth studying the separation order in more detail, so as to obtain a specific set of heuristics for the separation order of 3C-ISMB cascades.

For the sake of simplicity, in the following the complete separation of a ternary mixture subject to ideal and linear adsorption behavior is studied. Under this assumption the optimal operating point for the first stage in the \((m_{II}, m_{III})\)-plane and the \((m_{I}, m_{IV})\)-plane, respectively, corresponds to the tip of the triangle delimited by \( H_A \) and \( H_P \) (\( H_P \) and \( H_C \)), and to the vertex of the rectangular region delimited by \( H_A \) and \( H_C \) (\( H_A \) and \( H_C \)) for the case of extract (raffinate) coupling. The optimal operating points for the second stage are derived in the same manner and the full set of optimal operating points for both stages and both coupling strategies are comprehensively illustrated in figure 5.3a.

As a result, all \( m \)-values in equations (5.3) to (5.7) can be replaced by the corresponding Henry’s constants. Furthermore, constant values for the parameters pressure drop factor \((\phi=0.034 \text{ bar min cm}^{-2})\), maximum allowable pressure drop \((\Delta P_{\text{max}}=40 \text{ bar})\), overall void fraction \((\epsilon^*=0.68)\), and column length \((L=15 \text{ cm})\) are assumed for both stages. It is worth noting that the assumption on the column length requires to re-scale the second stage via the column diameter. Finally, the total number of columns \( n_{\text{tot}} \) in both stages is assumed to equal three, i.e. both 3C-ISMB stages are operated in the standard three-column configuration.

With the assumptions given above, one can readily calculate the optimal switching times of both stages from equation (5.3a), the re-scaling factor from equation (5.5a) or (5.5b) for
extract or raffinate coupling, respectively, which finally allows for calculating the overall cascade productivity from equation (5.7) assuming $c_{P,F,1}=1 \text{ g/l}$. In order to answer the question which separation should be performed first, one can now do this exercise for fixed values of $H_A$ and $H_C$ whilst varying $H_P$. This variation is best expressed through

$$\delta = \frac{(H_P - H_A)}{(H_C - H_A)} \tag{5.10}$$

where $\delta$ is a parameter running from 0 to 1, $\delta = 0$ ($\delta = 1$) meaning that there is no selectivity between A and P (P and C). Furthermore, it is worth mentioning that both separations are equally difficult if the selectivities between A and P, and between P and C, are equal, which is the case if $H_P = \sqrt{H_A H_C}$.

Figure 5.3b shows the separation performance versus the parameter $\delta$ for both extract and raffinate coupling using a fixed value for $H_A = 1$ and different fixed values for $H_C$, namely $H_C = 2, 3, \ldots, 8$. The $\delta$-value for equal selectivities is decreasing from 0.41 ($H_C=2$) to 0.26 ($H_C=8$). This relatively easy analysis demonstrates that the simple heuristic, proposing to perform the easy separation first, fails in finding the optimal coupling strategy of 3C-ISMB units, especially when the difference of $H_A$ and $H_C$ is large. In these cases, it is beneficial to remove the most retained component first even if the split between A and P is easier. Only in case where the removal of the light component from P and C is significantly easier, i.e. $\delta$-values of about 0.6 or higher, the extract coupling and consequently the carry-over of component C to stage 2 might make sense. Moreover, it is worth mentioning that the productivity of the raffinate coupling case is generally higher than the extract coupling scheme, i.e. if possible the chromatographic system should be tuned to yield $\delta$-values of about 0.3 to 0.4.
5.4 Experimental Part

After the theoretical study of the previous section, the remaining part of this chapter addresses the separation of the four stereoisomers of Nadolol, which are denoted as A, B, P, and C, i.e. in order of increasing retention, to be consistent with the notation of the previous section. Specifically, it is aimed at purifying the third component, labelled P, while treating the first two components, A and B, collectively as light impurities, and the fourth component, C, as heavy impurity.

The experimental procedures from the solvent composition screening, to the determination of the competitive adsorption isotherm, to the implementation of the 3C-ISMB cascade are described in the following section. Next, the relevant information on the experimental equipment and the materials used in this work is given.

5.4.1 Experimental Methods

From the literature [74], it was known that all four Nadolol stereoisomers can be resolved on Chiralpak AD using Heptane/Ethanol/Diethylamine (DEA) as mobile phase. Therefore, the first step of the design methodology can be skipped and one can directly move to the second step, i.e. the characterization of the linear retention behavior. This was done by studying diluted pulse injections and determining the retention times of the four stereoisomers for different ratios of Heptane and Ethanol and a fixed DEA content of 0.3% (v/v). The Henry’s constant of component $i$, $H_i$, can thus be calculated as follows:

$$H_i = \frac{\epsilon^*}{1 - \epsilon^*} \frac{t_{R,i} - t_0}{t_0} \quad (i = A, B, P, C)$$  (5.11)

where $t_{R,i}$ is the retention of component $i$ and $t_0$ the residence time of an unretained component, both corrected for the extra-column dead time. The residence time of an unretained component, $t_0$, was determined by diluted pulse injections of a 1,3,5-Tris-tert-butylbenzene solution which is considered to be unretained. Finally, the overall void fraction is calculated from

$$\epsilon^* = \frac{t_0 Q}{V}$$  (5.12)

where $Q$ is the volumetric flow rate and $V$ the column volume.

Based on the solvent screening, a mobile phase composition of Heptane/Ethanol/DEA 30/70/0.3 (v/v/v) was selected.

In the next step, the adsorption isotherm is measured by frontal analysis (FA) which is generally accepted as the most accurate method to determine competitive isotherms [60]. FA experiments of chiral compounds require, however, fraction collection and offline analysis of the collected fractions since the signal of online detectors, such as UV- or RI-detectors, are identical for all components. Therefore, a fraction collector was coupled to the column outlet and 80 fractions at a fixed sampling interval of 0.3 min were collected. For all FA experiments 4 ml of Nadolol solution at different concentrations are injected and a fixed flow rate of 0.5 ml/min was applied. Furthermore, the coupling to the fraction
CHAPTER 5. 3C-ISMB: CASCADE OPERATION

Collector is done via a T-connection so as to enable online dilution by supplying fresh solvent from an external pump. The flow rate of the external pump was fixed at 4.8 ml/min, i.e. a dilution factor of 10.6 was used, which guarantees that the concentrations of the resulting fractions are within the linear range of the calibration curve.

Next, the boundaries of the complete separation region in the \((m_{\text{II}}, m_{\text{III}})\)-plane are calculated from the parameters determined through FA, afterwards an appropriate operating point in terms of \(m\)-values is selected and the switching time as well as the step ratio are determined from equation (5.3). It is worth mentioning that the experimental set-up does not allow to run both stages of the 3C-ISMB cascade simultaneously, hence the first stage removing component C from the other three components was run first. Once cyclic steady state was achieved, the raffinate product was collected in a buffer tank until enough intermediate product for studying the second stage was obtained. Then, the operation was stopped, the plant was carefully flushed and the intermediate product was reprocessed on the same equipment using the same design methodology so as to produce the purified target component P in the extract.

The next sections provide the details about the experimental equipment and the materials used in this work.

5.4.2 Experimental set-up

Analytical set-up

All analytical measurements were carried out on an Agilent HPLC unit (Agilent Technologies 1200 Series, Palo Alto, CA, USA) using a Chiralpak AD-H column (25 cm × 0.46 cm, 5 µm, Chiral Technologies Europe, Illkirch, France) and Heptane/Ethanol/DEA 30:70:0.3 (v/v/v) as the mobile phase. The column was thermostated at 23°C and a volumetric flow rate of 0.5 ml/min was applied. The chromatograms were recorded with a UV-detector at 240 nm (bandwidth of 8 nm).

The frontal analysis experiments are carried out on the same HPLC unit that is additionally equipped with a manual 5 ml injection loop (Rheodyne 7725i, Rohnert Park, CA, USA). The loop is connected to the data acquisition software (Agilent ChemStation for LC 3D systems Rev. B.04.02 SP1 [208], Palo Alto, CA, USA) so as data acquisition automatically starts when the loop is manually switched to the injection position. All FA experiments are carried out on a Chiralpak AD column (15 cm × 0.46 cm, 20 µm, Chiral Technologies Europe, Illkirch, France) that is also used in the 3C-ISMB plant. The same mobile phase composition, temperature and flow rate as described above for the analytical measurements is applied. In order to decrease the band broadening due to the sample loop, the injection protocol proposed by Coq et al. [75] is applied, i.e. the injection loop is manually closed after 8:00 min which corresponds to an injection volume of 4 ml. Fractions at an interval of 0.3 min are taken using an auto fraction collector (GILSON FC 203B, Middleton, WI, USA). The fractions are online diluted by means of an external pump (515 HPLC Pump, Waters, Milford, MA, USA).
3C-ISMB plant

The separation is carried out on a modified ÄKTA™ explorer 100 system (GE Healthcare Europe GmbH, Freiburg, Germany). The program controlling all the devices is based on the standard UNICORN™ software (GE Healthcare Europe GmbH, Freiburg, Germany). The unit is equipped with three or four Chiralpak AD columns (15 cm × 0.46 cm, 20 µm, Chiral Technologies Europe, Illkirch, France), since all first stage separations are carried out in 1-1-1 3C-ISMB configuration, but for the second stage a 1-2-1 configuration is also studied.

More details on the experimental set-up is given in chapter 4, it is however worth noting that the plant was slightly modified for the present work. Namely, the orientation of the columns was changed from vertical to horizontal which allows significantly reducing the length of the connecting tubing parts. In this way, the same small value of extra-column dead volume of $V_D = 0.09$ ml could be achieved without the need for using tubing of very small inner diameter, i.e. green PEEK tubing (Upchurch Scientific, Oak Harbor, WA, USA) of 0.03 in inner diameter instead of red PEEK tubing of 0.005 in inner diameter could be used. As a result, the pressure drop along the tubing is now negligible. The linear pressure drop factor in Darcy’s law, $\phi$, slightly increased over time, however, its value was always about 0.05 bar min cm$^{-2}$. Finally, it is worth noting that the extra-column dead volume was taken into account according to the method described earlier (see chapter 4 and [22, 58]).

5.4.3 Materials

All materials used in this work, i.e. Nadolol, 1,3,5-Tris-tert-butylbenzene, Diethylamine (analytical grade), Heptane (analytical grade), and Ethanol (analytical grade) were bought from Sigma-Aldrich (Sigma-Aldrich Chemie GmbH, Buchs, Switzerland) and used without further purification. Additionally, analytical grade Ethanol from Scharlau (Scharlab S.L., Sentmenat, Spain) was used for some experiments. Detailed information on the CSP used is given above.

5.5 Results and Discussion

In the following section the results of the mobile phase screening are discussed first, before giving the results of the frontal analysis experiments. Afterwards, the individual stages of the 3C-ISMB cascade are discussed separately, and finally the overall performance of the cascade operation is discussed.

5.5.1 Screening of mobile phase composition

The separation of Nadolol in Heptane/Ethanol/DEA or Hexane/Ethanol/DEA on Chiralpak AD has already been studied perviously [74]; there it was shown that both solvent combinations are suitable to resolve all four stereoisomers; however, Heptane was shown
to yield generally a better resolution as compared to Hexane. Moreover, the previous work demonstrated that retention times of all four component decrease as the Ethanol content increases, as expected.

Based on these findings, it was decided to examine the retention behavior of the Hexane/Ethanol system only. More precisely, the effect of the Ethanol content was studied and the effect of the DEA content was checked. The latter showed that a small amount of DEA is indeed necessary to resolve the stereoisomers, but within reasonable ranges of the basic modifier no effect on the retention behavior is observed. Hence, the DEA content was fixed at 0.3 vol% as done previously, and only the Ethanol content was varied in the following, namely from 15 vol% to 70 vol%.

In figure 5.4 the resulting Henry’s constant are plotted against the Ethanol content in a double-logarithmic plot according to the Soczewinski equation \[ \log H_i = a_i \log v_{\text{EtOH}} + b_i \] (5.13)

where \( v_{\text{EtOH}} \) is the volume percent of Ethanol and \( a_i \) and \( b_i \) are fitting parameters for each component \( i \), their numerical values being given in table 5.1.

The Soczewinski plot confirms earlier results [74], namely that all isomers are separated and that their Henry’s constants significantly decrease as the Ethanol content increases.

<table>
<thead>
<tr>
<th>Component</th>
<th>A</th>
<th>B</th>
<th>P</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>( a_i )</td>
<td>-1.67</td>
<td>-1.78</td>
<td>-1.74</td>
<td>-1.73</td>
</tr>
<tr>
<td>( b_i )</td>
<td>6.82</td>
<td>7.62</td>
<td>8.01</td>
<td>8.85</td>
</tr>
</tbody>
</table>

Table 5.1: Parameters of the Soczewinski equation (see als figure 5.4).
Furthermore, the plot shows that all four components are similarly affected by the Ethanol content, i.e. the selectivities remain almost constant over the whole range of Ethanol contents studied. It is worth noting that the Soczewinski equation regresses fairly well the dependence of Henry’s constants on the mobile phase composition, since all regression lines have a value of $R^2$ of 0.999.

The Soczewinski plot, finally, allowed for determining the solvent composition that yields Henry’s constants within the desired range. Namely the solvent composition Heptane/Ethanol/DEA 30:70:0.3 (v/v/v) was identified as the best compromise between acceptable retention and good resolution for the first stage experiment. For the sake of illustration a chromatogram of a diluted pulse injection is shown in figure 5.4b; the Henry’s constant for the corresponding solvent composition are $H_A = 0.76$, $H_B = 1.06$, $H_F = 1.82$, and $H_C = 4.48$.

5.5.2 Competitive quaternary adsorption isotherm

An amount of 4 ml of a quaternary mixture containing all Nadolol stereoisomers was injected on a 3C-ISMB column, at the total feed concentrations of 5 g/l, 10 g/l, 15 g/l, and 20 g/l. The individual elution profiles of each component were afterwards derived from the offline analysis of the collected fractions (see section 5.4.2) and are given in figures 5.5a (component A) to 5.5d (component C). Based on these measurements, the Henry’s constants and equilibrium constants of a four-component competitive Langmuir isotherm were fitted applying the inverse peak fitting method [60], using the Matlab built-in genetic algorithm routine. This method is based on minimizing the difference of simulated and experimental elution profiles by adjusting the isotherm parameters, i.e. Henry’s constants $H_i$ and equilibrium constants $K_i$. For the simulation the transport dispersive model described in chapter 3 was used with fixed values for dispersion and mass transfer coefficients. The same values were assumed for all four components and are given below

$$\frac{\epsilon_b D_{ax}}{\epsilon^* u} = 5 \times 10^{-5} \text{ m}$$

$$k_s a_v = 1 \text{ s}^{-1}$$

where $\epsilon_b$ is the bed void fraction, $D_{ax}$ the axial dispersion coefficient, $u$ the superficial velocity, $k_s$ the mass transfer coefficient, and $a_v$ the specific surface of the particles. The resulting isotherm parameters are referred to as ”isotherm Q” and are given in table 5.2. Moreover, the solid lines in figures 5.5a to 5.5d represent the simulated elution profiles. The experimental profiles show shock transitions in adsorption and simple wave transitions in desorption as well as intermediate states that are typical of competitive Langmuirian systems. However, with reference to figures 5.5b and 5.5c it is worth noting, that two anomalies are observed. Firstly, the second intermediate state of component B is below the concentration of its feed state for all feed concentrations studied. Secondly, although the breakthrough of component B occurs before the breakthrough of component
Figure 5.5: Frontal Analysis of the quaternary mixture at a total feed concentration of (a) 5 g/l, (b) 10 g/l, (c) 15 g/l, and (d) 20 g/l. Open symbols represent the experimentally measured concentration profile by offline analysis of the collected fractions whereas the solid line represents the simulated concentrations profiles using the parameters of isotherm Q listed in table 5.2.
CHAPTER 5. 3C-ISMB: CASCADE OPERATION

<table>
<thead>
<tr>
<th>Component</th>
<th>A</th>
<th>B</th>
<th>P</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
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<td></td>
<td></td>
</tr>
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</tr>
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<td>0.055</td>
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<td>$K_i$</td>
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<td>0.098</td>
<td>0.103</td>
<td>-</td>
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</tbody>
</table>

Table 5.2: Isotherm parameters used for the design of the 3C-ISMB experiments.

P, the latter is completely eluted from the column before component B, i.e. the two desorption waves cross each other. Both phenomena become more pronounced as the feed concentration increases and neither can be described by a simple multi-component Langmuir model. It appears as if the presence of component C slowed down the desorption of component B, and a more complex isotherm model would be required to accurately describe all features of the experimental elution profile. However, the simple Langmuir model describes the system well enough since it captures all relevant composition fronts, namely front of A, tail of P, as well as front and tail of C, rather well. Therefore, isotherm Q will be used to design the first stage of the cascade (see section 5.5.4), however, since the presence of C influences the adsorption behavior of B the competitive adsorption isotherm of the intermediate product needs to be determined separately in order to design the second stage.

5.5.3 Competitive ternary adsorption isotherm

For the second stage separation the tail of component B, which is not very well described by isotherm Q, becomes crucial for the control of the purity of the final product P. Moreover, the results of section 5.5.2 provide evidence that component C, which is no longer present in stage 2, influences the adsorption behavior of component B in an unusual manner. Therefore, it is worth examining the adsorption of the ternary mixture, i.e. A, B, and P, separately. For that purpose, the solvent of the raffinate product of a first stage separation was evaporated completely so as to obtain the pure ternary mixture (content of component C below 0.5%) in dry form. The dry product was then dissolved in fresh solvent in order to obtain a solution with a total concentration of 8.7 g/l. This solution was afterwards used to perform a frontal analysis experiment and to determine new isotherm parameters, referred to as isotherm T, according to the same method as described in section 5.5.2. The resulting experimental and simulated elution profiles are represented in figure 5.6a. The figure shows that the anomalies observed for the quaternary mixture
Figure 5.6: Frontal Analysis of the ternary mixture at (a) a total feed concentration of 8.7 g/l using Heptane/Ethanol/DEA 30/70/0.3 (v/v/v), and (b) a total feed concentration of 1.9 g/l using Heptane/Ethanol/DEA 40/60/0.3 (v/v/v). Open symbols represent the experimentally measured concentration profile by offline analysis of the collected fractions whereas the solid line represents the simulated concentrations profiles using the parameters of isotherm T and T_{dil}, respectively, listed in table 5.2.

are no longer present and that isotherm T (parameters given in table 5.2) describes the experimental profiles very well. This isotherm was used to design experimental runs 2.1 to 2.3 (see figs. 5.8a to 5.8c and tab. 5.3).

Since the retention of component A, B, and P is relatively low with the given solvent composition, the dilution of the intermediate product with Heptane/DEA was also examined. From the Soczewinski plot one finds immediately that the Henry’s constant of component P can be increased to about 5 by using Heptane/Ethanol/DEA 60/40/0.3 as mobile phase. In order to study the competitive adsorption behavior of the ternary system in this new eluent, the raffinate product of experiment 1.4 (see table. 5.3) was thus diluted with Heptane/DEA so as to end up with the desired solvent composition (dilution factor of 1.75). The resulting solution had a total feed concentration of 1.89 g/l and was treated as described above so as to obtain the parameters of isotherm T_{dil} (see table 5.2) which was used to design experimental run 3 (fig. 5.8d and tab. 5.3).
### Table 5.3: Overview of all 3C-ISMB experiments performed.

<table>
<thead>
<tr>
<th>Run</th>
<th>$c_{P,s}$ [g/L]</th>
<th>Operating mode</th>
<th>Average Flow rate ratio $\tilde{\eta}$ [-]</th>
<th>$t^*$ [min]</th>
<th>$\alpha$ [-]</th>
<th>Flow rate $Q$ [mL/min]</th>
<th>Purity [%]</th>
<th>$PR_s$ [g/L h]</th>
<th>$SC_s$ [L/g]</th>
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<td>96.4</td>
<td>85.3</td>
<td>8.07</td>
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<td>0.57</td>
<td>4.68 1.67 2.67 3.04</td>
<td>99.7</td>
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<td>93.7</td>
<td>97.4</td>
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<td>0.65</td>
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<td>95.6</td>
<td>97.8</td>
<td>2.60</td>
<td>10.56</td>
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</table>
5.5.4 Experimental implementation of the 3C-ISMB cascade

In this section all first stage separation experiments are discussed first, then the second stage separation experiments are summarized, finally the performance of the whole cascade is assessed by applying the re-scaling concept outlined in section 5.3.2. Given the findings of section 5.3.3, a raffinate stream coupling scheme was implemented, i.e. component C was removed from the other three stereoisomers in stage one and target component P was recovered from the extract port of stage 2, where the feed was the raffinate product of stage 1.

First stage - Separation of C from A, B, and P

In total, four first stage separations with total feed concentrations ranging from 5 g/l to 15 g/l were performed as illustrated graphically in figure 5.7 and summarized in the first four rows of table 5.3 The product purities for this stage are defined as

\[
PU_{\text{Raff},1} = \frac{\sum_{i=A,B,P} \bar{c}_i,\text{Raff},1}{\sum_{i=A,B,P,C} \bar{c}_i,\text{Raff},1}
\]

(5.15a)

\[
PU_{\text{Ext},1} = \frac{\bar{c}_C,\text{Ext},1}{\sum_{i=A,B,P,C} \bar{c}_i,\text{Ext},1}
\]

(5.15b)

where \(\bar{c}_i,\text{Raff},1\) and \(\bar{c}_i,\text{Ext},1\) are the average concentrations of component i at steady state in the raffinate and the extract of the first stage, respectively.

The first experiment, i.e. 1.1, is clearly ill-designed, since the operating point in the \((m_{II}, m_{III})\)-plane is deeply in the impure extract region and additionally, \(m_1\) is below the Henry’s constant of component C; as a result both extract and raffinate are impure. Therefore, the 5 g/l experiment was repeated using a higher \(m_1\)-value and moving into the triangular region of complete separation (experiment 1.2), which resulted in purities of >99.4% for both streams as expected. Since this stage is mainly targeted at a highly pure raffinate product, the following two experiments at 10 g/l (experiment 1.3) and 15 g/l (experiment 1.4) were performed on the boarder of the impure extract region so as to maximize the distance to the impure raffinate region without significantly compromising yield. The resulting raffinate purities of 99.6% for both experiments and extract purities of 96% and 95%, respectively, are in good agreement with the expectations from Triangle Theory and demonstrate successfully the validity of our simplified design and simplified isotherm approach.

With reference to the last two columns of table 5.3, it is noted that the first stage of the present work is analogous to the previous work by Ribeiro et al. [74] where a 1-2-2-1 standard SMB plant was used for solving the same separation problem. A direct quantitative comparison of the performance reported in this work with the one reported earlier [74] is hampered by the fact that Ribeiro et al. applied a lower feed concentration of only 2 g/l. Nonetheless, it is worth pointing out that the present work achieved significantly higher productivities at significantly lower solvent consumption as compared
Figure 5.7: Region of complete separation in the \((m_2, m_3)\)-plane for the split ABP/C calculated from the parameters of isotherm Q (see table 5.2) for total feed concentrations of 5 g/l, 10 g/l, and 15 g/l. The corresponding operating points in \((m_1, m_4)\)-plane and \((m_2, m_3)\)-plane of experiments 1.1 to 1.4 are represented by circles (5 g/l), squares (10 g/l), and diamonds (15 g/l).

to their work [74], which is not only a result of the higher feed concentration but also of the novel, optimized operating mode.

For the second stage separations being discussed in the next section, the steady state raffinate products of experiments 1.3 and 1.4, were reprocessed in stage 2 so as to isolate the target component P. The raffinate of experiment 1.1 was not further processed due to low purity, which *a priori* impedes our target of producing a pure component P stream. Finally, the raffinate of experiment 1.2 was utilized to determine the ternary competitive adsorption isotherm, hence only study the overall cascade performance for initial total feed concentration of 10 g/l and 15 g/l can be studied.

**Second stage - Separation of P from A and B**

The second stage is intended chiefly for producing a highly pure extract stream consisting of component P only, therefore the purities for this stage are defined as

\[
PU_{\text{Raff},2} = \frac{\sum_{i=A,B} \bar{c}_{i,\text{Raff},2}}{\sum_{i=A,B,P,C} \bar{c}_{i,\text{Raff},2}} \quad (5.16a)
\]

\[
PU_{\text{Ext},2} = \frac{\bar{c}_{P,\text{Ext},2}}{\sum_{i=A,B,P,C} \bar{c}_{i,\text{Ext},2}} \quad (5.16b)
\]
where $\bar{c}_{1,\text{Raff},2}$ and $\bar{c}_{1,\text{Ext},2}$ are the average concentrations of component $i$ at steady state in the raffinate and the extract of the second stage, respectively. Note further that the denominator also includes component C so as to account for the small amount (\(<0.5\%\)) of C carried over from stage 1.

All second stage experiments are illustrated in figures 5.8a to 5.8d as well as summarized in table 5.3 (fifth to last row). With reference to figures 5.8a to 5.8d, it is worth noting that operating points were now chosen close to the boarder of the impure raffinate region or within the impure raffinate region, since the main interest is now in obtaining a highly pure extract.

In experiments 2.1 (fig. 5.8a) and 2.2 (fig. 5.8b) the separation of the intermediate product of experiment 1.3 was studied, which had a total feed concentration of 2.54 g/l. For both series three operating points labeled (a), (b), and (c) are studied and operating point (b) was studied both in open and closed loop configuration. However, whereas experiment 2.1 was carried out in the usual 1-1-1 configuration, experiment 2.2 was operated in 1-2-1 configuration so as to improve the extract purity. The intermediate product of experiment 1.4 having a higher total concentration, i.e. 3.31 g/l, was studied in experiment 2.3 (fig. 5.8c), which was as well operated in 1-2-1 configuration and three similar operating points with respect to the triangle boundaries were examined. Finally experiment 3 (fig. 5.8d) was carried out using the diluted raffinate of experiment 1.4 so as to obtain the eluent composition corresponding to isotherm $T_{dil}$ and hence a larger region of complete separation.

It is worth discussing only experiment 2.1 in more detail, since similar trends are observed in experiments 2.2 and 2.3. With reference to figure 5.8a and table 5.3 it can be noted that the raffinate (extract) purity decreases (increases) when moving from operating point (a) to operating point (b) as expected from Triangle Theory. The decrease in raffinate purity is significant since the operating point moves from just within the region of complete separation to a position within the impure raffinate region, however, the extract purity only slightly increases from 94.4\% to 96.0\%. Since the extract is not only polluted from component B, but also from component A due to the recycle in substep 2, the purity can be further increased to 97.5\% by performing operating point (b) in open loop configuration. It is, however, worth noting that the open loop operation significantly compromises solvent consumption and yields a highly diluted raffinate product. Therefore, the raffinate product of the open loop runs were not worth sampling and were directly disposed of without further analysis. Since the open loop configuration yielded a higher extract purity, a further experiment (c) with a lower $m_4$-value was performed and additionally the operating point in the $(m_H, m_H)$-plane was moved closer to the diagonal and within the region of complete separation. As a result, the raffinate purity increased as expected, however, the extract purity was only slightly better as compared to closed loop point (b). In conclusion all effects observed in experiment 2.1 are in good agreement to theory, however, the extract purities remained below the targeted complete separation. Adding a second column in section 2 and repeating the four experiments described above in 1-2-1 configuration (experiment 2.2) resulted in the expected improvement of the extract purity,
Figure 5.8: Region of complete separation in the \((m_2, m_3)\)-plane for the split AB/P calculated from the parameters of isotherm \(T\) ((a)-(c)) and isotherm \(T_{\text{dil}}\) ((d)) (see table 5.2) for total feed concentrations of: (a) 2.5 g/l, (b) 2.5 g/l, (c) 3.3 g/l, and (d) 1.9 g/l. The corresponding operating points in \((m_1, m_4)\)-plane and \((m_2, m_3)\)-plane of experiments 2.2 to 3 are represented by circles (operating point (a)), squares (operating point (b)), and diamonds (operating point (c)). Note that the eluent composition for the experiments represented in figure (d) differs from the other three subplots.
however, at the expense of productivity. The highest extract purity of all second stage experiments (98.3%) was indeed achieved in experiment 2.2(b) in open loop configuration. Finally, experiment 2.3 confirmed the observations of previous experiments for a higher feed concentration.

For experiment 3 the raffinate of experiment 1.4 was diluted with Heptane/DEA so as to obtain a 1.89 g/l solution in Heptane/Ethanol/DEA 60/40/0.03 (v/v/v). The results are listed in the last two lines of table 5.3 and demonstrate that diluting results in (i) significantly higher extract purities at larger productivity as compared to undiluted runs in 1-1-1 configuration, (ii) higher purities and higher productivities as compared to closed loop 1-2-1 configuration, and (iii) comparable values of specific solvent consumption. In conclusion, the diluting scheme offers considerable and unexpected benefits, which is attributed to the larger region of complete separation making the separation more robust, and to the reduced viscosity due to the higher Heptane content allowing compensating the dilution with higher volumetric flow rates.

**Overall performance**

With the results from sections 5.5.4 and 5.5.4 one is now able to calculate the performance of the fully integrated cascade applying the re-scaling concept described in section 5.3.2. The resulting re-scaling factors for experiments 2.1 to 3 as well as the corresponding overall productivities and specific solvent consumptions are summarized in table 5.4. With reference to experiment 3 it is worth noting that the dilution of the intermediate product has to be properly accounted for, both in calculating the re-scaling factor as well as the overall solvent consumption, i.e. equations (5.5b) and (5.9) modify to

\[
\begin{align*}
  r_{\text{case2,dil}} &= f_{\text{dil}} \frac{\hat{Q}_{3,1} - \hat{Q}_{4,1}}{\hat{Q}_{3,2} - \hat{Q}_{2,2}} = f_{\text{dil}} \frac{\hat{r}_2 (m_{3,1} - m_{4,1})}{\hat{r}_1 (m_{3,2} - m_{2,2})} \\
  SC_{\text{dil}} &= \frac{\hat{Q}_{D,1} + r_{\text{case2,dil}} \hat{Q}_{D,2} + \hat{Q}_{F,1} + (f_{\text{dil}} - 1) \hat{Q}_{\text{Raff},1}}{\hat{Q}_{\text{FCP,F,s}}} 
\end{align*}
\]

where \(f_{\text{dil}}\) represents the dilution factor and \(\hat{Q}_{\text{Raff},1}\) the average volumetric raffinate flow rate of stage 1.

Table 5.4 shows that the column dimensions of the second stage need to be significantly larger as compared to stage 1, as a result the overall performance metrics \(PR\) and \(SC\) are chiefly determined by the performance of the second stage. This stems from the fact that productivities are weighted with the amount of stationary phase required, i.e. the stage performance of the up-scaled second unit is equal to those reported in table 5.3 for the unscaled case. Although, one needs to consider also the amount of the stationary phase and solvent used in stage 1, for the overall cascade performance, the latter is only slightly worse as compared to stage performance of stage 2. This stems from the fact that the column dimensions of the first stage are substantially smaller, i.e. stage 1 has only a minor influence on the overall cascade performance.
In conclusion this analysis demonstrates that the design of 3C-ISMB should be focused on optimizing the performance of the second stage. Therefore, the use of two columns in section 2 (configuration 1-2-1 instead of 1-1-1) as well as operating close to the diagonal (operating point (c) in experiments 2.1 to 2.3) should be avoided. Additionally, it is worth pointing out that diluting the intermediate product with Heptane/DEA results not only in the highest product purity of all closed loop experiments, but also in the lowest re-scaling factor and highest overall cascade productivity without compromising solvent consumption too much. Finally, it is noted that further improvements might be achieved by increasing the concentration of the intermediate product stream, i.e. by optimizing the operating point in the \((m_1, m_{IV})\)-plane of stage 1.

### Table 5.4: Performance of the overall 3C-ISMB cascade applying the re-scaling approach (see section 5.3.2).

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<th>(SC) [L/g]</th>
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<td></td>
<td>Cascade (b),O</td>
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5.6 Conclusions

This work studied the implementation of a 3C-ISMB cascade for chromatographic three-fraction separation. A general design methodology was proposed and guidelines for process design based on Triangle Theory and a re-scaling approach were derived. The latter accounts for the fact, that the feed flow rates to the second stage are generally higher due to dilution in stage 1, which can be compensated for by using larger column dimensions. In contrast to fully integrated ternary SMB processes, such as the 8-zone SMB [40] or the JO process [46, 47], cascade operation gives more flexibility and allows for different columns dimensions. This flexibility is exploited by applying the re-scaling concept, which enables to run both stages under optimal conditions with respect to switching time.
and step ratio. Furthermore, heuristics on the separation order were developed, which demonstrated that it is in most cases beneficial to couple the two stage via the raffinate stream of stage 1. Only in cases where the selectivity between light impurities and target component is substantially higher than the selectivity between target component and heavy impurities, an extract coupling scheme might be beneficial.

In the following experimental part, the design methodology was validated studying the purification of an intermediately retained stereoisomer of Nadolol, from an equimolar mixture of its four stereoisomers. To the best of our knowledge, the present work is the first experimental study on this kind of chiral separation problem. The separation was carried out under non-linear chromatographic conditions on Chiralpak AD using Heptane/Ethanol/DEA as mobile phase. In order to design the experiments a solvent screening varying the ratio of Heptane and Ethanol was performed first, thus showing that all four components are resolved and that their Henry’s constants are strongly dependent on the Ethanol content, which is well described by the Soczewinski equation. Afterwards, the competitive adsorption isotherms of quaternary and ternary Nadolol solutions were derived, yielding a good agreement with the multi-component Langmuir model.

Finally, a total number of 18 3C-ISMB experiments was performed thus demonstrating (i) good agreement with the prediction from Triangle Theory, (ii) high product purity and productivities in the first stage, and (iii) target product purities of up to 98.3%. Furthermore, the best compromise between product purity and overall cascade performance could be achieved by adapting the solvent composition between the two stages, which resulted in 97.8% product purity and an overall cascade productivity of 2.10 g/(lh), requiring a specific solvent consumption of 12 liters per gram of product.

5.7 Nomenclature

\[ a_v \] Specific surface of the adsorbent particles [cm\(^{-1}\)]
\[ a_i, b_i \] Parameters in Soczewinski equation [-]
\[ c_{P,F,s} \] Concentration of target component \( P \) in feed stream of stage \( s \) [g l\(^{-1}\)]
\[ \bar{c}_{i,e,s} \] Average concentration of component \( i \) in external stream \( e \) of stage \( s \) [g l\(^{-1}\)]
\[ D_{ax} \] Axial dispersion coefficients [cm\(^2\) s\(^{-1}\)]
\[ \Delta P_{\text{max},s} \] Maximum allowable pressure drop in stage \( s \) [bar]
\[ f_{\text{dil}} \] Dilution factor [-]
\[ H_i \] Henry’s constant of component \( i \) [-]
\[ K_i \] Equilibrium constant of component \( i \) [l g\(^{-1}\)]
\[ k_s \] Mass transfer coefficient [s\(^{-1}\)]
\[ L_s \] Column length in stage \( s \) [cm]
\[ m_{j,s} \] Dimensionless flow rate ratio in section \( j \) of stage \( s \) [-]
\[ n_{\text{tot},s} \] Total number of columns in stage \( s \) [-]
\[ n_{j,s} \] Number of columns in section \( j \) of stage \( s \) [-]
\[ PR \] Overall cascade productivity [g l\(^{-1}\) h\(^{-1}\)]
\[ PR_s \] Productivity of stage \( s \) [g l\(^{-1}\) h\(^{-1}\)]
CHAPTER 5. 3C-ISMB: CASCADE OPERATION

PU_{e,s}  Purity of external stream \( e \) of stage \( s \) [%]

\( Q \)  Volumetric flow rate [ml min\(^{-1}\)]

\( Q_{e,s} \)  Average volumetric flow rate of external stream \( e \) of stage \( s \) [ml min\(^{-1}\)]

\( Q_{j,s} \)  Volumetric flow rate in section \( j \) of stage \( s \) [ml min\(^{-1}\)]

\( Q'_{j,2} \)  Average volumetric flow rate in section \( j \) of an unscaled stage 2 [ml min\(^{-1}\)]

\( r \)  Re-scaling factor [-]

\( SC \)  Overall cascade solvent consumption [l g\(^{-1}\)]

\( SC_s \)  Solvent consumption of stage \( s \) [l g\(^{-1}\)]

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

\( t_0 \)  Residence time of an unretained component \( i \) [min]

\( t^*_s \)  Switching time in stage \( s \) [min]

\( u \)  Superficial velocity [cm min\(^{-1}\)]

\( V_D \)  Total extra-column dead volume per section [ml]

\( v_{\text{EtOH}} \)  Ethanol content in mobile phase [vol%]

\( V_s \)  Column volume in stage \( s \) [ml]

Greek Letters

\( \alpha_s \)  Step ratio in stage \( s \) (\( 0 \leq \alpha_s \leq 1 \)) [-]

\( \delta \)  Parameter characterizing the relative selectivity [-]

\( \epsilon^*_s \)  Overall void fraction in stage \( s \) [-]

\( \epsilon_b \)  Bed void fraction [-]

\( \phi_s \)  Pressure drop factor in Darcy’s law for stage \( s \) [bar min cm\(^{-2}\)]

Subscripts and Superscripts

A  Weakest retained component

B  Intermediately retained component

C  Strongest retained component

case1  Extract coupling

case2  Raffinate coupling

D  Desorbent
dil  Diluted

Ext  Extract
e  Index for external stream (\( e=\text{D,Ext,F,Raff} \))

F  Feed

i  Component index (\( i=\text{A,B,C,P} \))

j  Section index (\( j=\text{I,II,III,IV} \))
P  Intermediately retained target component

max  Maximum allowable
Raffinate

Stage index ($s=1,2$)
Conclusion and Outlook

This thesis studied several modifications of the intermittent simulated moving bed (I-SMB) technology aiming at both extending the technology to allow for continuous chromatographic three-fraction separation and improving the performance of classical binary separations. Although the I-SMB process was shown to significantly outperform classical SMB [22, 36], further improvements were achieved in this work, since it was found that original I-SMB does not fully exploit the stationary phase. More specifically, section IV is completely idle for a relatively large fraction of the switching period and section I is almost completely regenerated at the time when section IV is reconnected to the column train. In other words, roughly a fourth of stationary phase is not actively contributing to the separation. Therefore, the surplus stationary phase can either be used for accommodating an additional separation zone so as to enable three-fraction separation, or it can be removed in order to enhance the separation performance of binary separations. The former optimization pathway was followed in chapter 2 to yield two modified I-SMB process concepts, termed 3S-ISMB and 3W-ISMB; whereas subsequent chapters were dedicated to the latter pathway yielding the so-called 3C-ISMB process.

In chapter 2, it was shown how the four-section I-SMB concept can be extended to three-fraction separations by withdrawing an additional product stream during the previously nonproductive substep 2. In general, it is possible to recover either the strongest or the weakest retained component of a ternary mixture during substep 2. Both options were explored and the resulting process schemes were accordingly termed 3S-ISMB and 3W-ISMB, respectively. These two processes were analyzed in the framework of the equilibrium theory of chromatography thus showing that both processes can be designed through application of a modified Triangle Theory. More specifically, the region of complete separation under linear chromatographic conditions is defined by a triangle in the \((m_\Pi, m_\III)\)-plane, whose boundaries are determined by the Henry’s constants of the com-
ponents recovered in substep 1. In addition a critical line with slope -1 (+1) for 3S-ISMB (3W-ISMB) and an n_{3,1}-axis intercept depending on the Henry’s constants, determines which part of the triangle is accessible for complete separation of the ternary mixture. As a result, 3S-ISMB becomes infeasible if the critical line intersects the diagonal below the triangle and hence requires rather large selectivities to be applicable. For the 3W-ISMB in contrast, feasibility is always guaranteed, however, for low-selectivity systems, the accessible region of complete separation gets rather narrow, which in turn compromises feed flow rates. The latter is a physical limitation indeed caused by the difficulty of such separation problems and inherent to any chromatographic three-fraction separation process.

It is worth pointing out that the methodology presented in this thesis facilitates to choose between 3S-ISMB and 3W-ISMB. Furthermore, it enables a simple and fast assessment of the potential performance of the two processes for any given separation problem. In addition, the potential of the 3W-ISMB process has been demonstrated successfully by experimentally studying the separation of a mixture of the enantiomers of γ-Phenyl-γ-butyrolactone and the (-)-Tröger’s Base enantiomer in pure ethanol on Chiralpak AD, which yielded product purities of at least 94% for all three product streams.

In chapter 3, the 3C-ISMB process for binary separations was theoretically introduced and comparatively assessed against conventional I-SMB by means of a thorough simulation study. It was shown that the classical function of sections I and IV, i.e. regeneration of stationary and mobile phase, can be combined within a single section without compromising purity. As a result, the number of columns can be reduced from four to three, which allows for a higher volumetric flow rates during substep 2 as compared to an analogous I-SMB process using columns of equal lengths. Therefore, the step ratio of 3C-ISMB is larger than that of the corresponding I-SMB process, which yields eventually a larger throughput at a reduced amount of stationary phase and thus significant improvements in terms of productivity. In an extensive simulation study, it was shown that 3C-ISMB can be easily designed by the well-known Triangle Theory which is an important advantage compared to other SMB schemes using non-constant operating conditions which usually require numerical optimization strategies. Finally, the comparative assessment against I-SMB resulted in an increase of productivity by as much as 60% without significantly sacrificing solvent consumption. Given that I-SMB was previously shown to outperform standard SMB by a factor 2 [22], it can thus be concluded that changing from the still widely applied standard SMB to 3C-ISMB would boost productivity by a factor 3.

In chapter 4, the 3C-ISMB process was experimentally implemented studying the separation of racemic Tröger’s Base in pure ethanol on Chiralpak AD. Furthermore, the experimental process performance was directly compared to a corresponding I-SMB process, thus confirming the theoretically derived improvements from chapter 3. More specifically, it was shown that 3C-ISMB delivers the same high product purities as I-SMB, however, at a significantly higher productivity. Therefore, this thesis did not only demonstrate substantial improvements arising from the adaption of the new operating mode but also a rather easy implementation of this new operation mode. Finally, chapter 5 exploited the benefits of the 3C-ISMB process by incorporating it into
a cascade separation process thus allowing for three-fraction separation. A general design methodology for 3C-ISMB cascades based on Triangle Theory was proposed. The latter makes full use of the flexibility offered by the cascade concept by allowing for both changing the solvent composition between the two stages and employing different column dimensions in stage 2 as compared to stage 1. The design methodology was experimentally validated by studying the purification of an intermediately retained stereoisomer of Nadolol, from an equimolar mixture of its four stereoisomers. The experiments demonstrated (i) good agreement with the prediction from Triangle Theory, (ii) high product purity and productivities in the first stage, and (iii) target product purities of up to 98.3%.

Thus summarizing, this thesis has convincingly demonstrated that continuous binary separations using only three chromatographic columns are possible through the adaption of the new 3C-ISMB process. The novel operating mode was furthermore shown to significantly outperform I-SMB when assuming that both processes are operated with columns of equal lengths. In addition, three process options for three-fraction separation were proposed and successfully validated experimentally. Both achievements are important regarding the potential of multi-column chromatography for industrial separation of chiral compounds. More specifically, the former allows for reduced equipment costs and decreased labour effort for column repacking when switching production campaigns thus making chromatography more competitive against alternative separation processes. The latter, significantly extends the potential field of application since a three-fraction separation process allows in principle for recovering a target product from any multi-component mixture.

It is worth pointing out that the comparison of process performances both in this thesis as well as in the previous work on I-SMB \[22, 36\] was restricted to the assumption of constant column length, i.e. a typical case if retrofits of existing units are concerned. Therefore, the previous work by Katsuo \[22, 36\] demonstrated that the performance of an existing SMB plant can be substantially improved by adapting the I-SMB concept, whereas this thesis showed that even further improvements are possible by implementing the 3C-ISMB concept, e.g. by modifying an existing 1-2-2-1 SMB unit into two simultaneously operated 3C-ISMB units with alternating substep order. However, it remains open whether similar improvements were obtained if the column length was allowed to vary in a full optimization, which could be the objective of a future work.

As a concluding remark, I believe that the ever increasing number of column configurations and operating modes emerging for both binary and three-fraction separations is cementing the perception of multi-column chromatography as a complicated and difficult process. In this respect, the processes, design methodologies and performance assessments presented in this thesis clearly have their merits since they are easy to understand owing to the fact that simple and well-known short-cut methods are applicable.
Excursus: Challenges in the quantitative description of the delta-shock phenomenon

7.1 Introduction

The delta-shock is a new type of composition front in nonlinear chromatography that has been added to the family of classical transitions, i.e. simple waves, shocks and semi-shocks [51]. It can be viewed as a growing travelling spike superimposed to the discontinuity separating the initial and the feed state, which propagates along the column at constant speed and constant rate of growth.

The occurrence of delta-shocks in the case of mixed competitive-cooperative isotherms, where the weak retained component is Anti-Langmuirian whilst the strong retained component is Langmuirian, was first predicted theoretically and their behaviour was analyzed in the frame of equilibrium theory of chromatography [51]. Later, these findings were experimentally complemented by providing evidence that the binary system consisting of Phenetole (weak retained, Anti-Langmuirian component) and 4-tert-Butylphenol (strong retained, Langmuirian component) in methanol-water (63/37 v/v) on a Zorbax 300SB-C18 column exhibits a delta-shock when Phenetole initially saturating the column is displaced by 4-tert-Butylphenol, both at high feed concentrations [52].

This side project of my Ph.D. was initially aimed at confirming and quantitatively describing the earlier results [52]. Therefore, the single-component adsorption isotherms characterizing the two species claimed to result in a delta-shock were accurately measured by frontal analysis. Furthermore, the displacement experiments reported earlier [52] were reproduced and additional experiments, where interactions between classical transitions believed to result in a delta-shock, were studied. However, these studies revealed a cou-
ple of inconsistencies in the previous work [52], which in fact provided evidence that the interpretation of the earlier results needs to be overthrown. Most importantly, it was conjectured that the Phenetole - 4-tert-Butylphenol system does not result in the occurrence of delta-shocks, which was recently confirmed through additional binary frontal analysis and displacement experiments. This brief excursus summarizes my work on the "delta-shock system" in a more or less chronological manner thus convincingly demonstrating that there is no experimental evidence of a delta shock as claimed in ref. [52].

7.2 Theoretical Background

7.2.1 Equilibrium Theory Analysis

The delta-shock can develop in binary chromatographic systems subject to a mixed competitive-cooperative Langmuir isotherm of the so-called M2 type, i.e.

\[ n_i = \frac{H_i c_i}{1 - K_i c_1 + K_2 c_2} \quad (i = 1, 2) \]  

(7.1)

where \( n_i \) and \( c_i \) are the adsorbed and fluid phase concentrations, respectively, whereas \( H_i \) and \( K_i \) are the Henry’s and equilibrium constants of component \( i \). The subscript 1 indicates the less retained Anti-Langmuirian component and the subscript 2 stands for the more retained Langmuirian component, i.e. \( H_1 < H_2 \).

The mathematical analysis presented in [51] showed that a delta-shock occurs when pure component 2 at concentration \( c_2 \) is fed to a column initially saturated with pure component 1 at concentration \( c_1 \) if and only if the following condition is fulfilled:

\[ \frac{n_1}{c_1} = \frac{H_1}{1 - K_1 c_1} > \frac{H_2}{1 + K_2 c_2} = \frac{n_2}{c_2} \]  

(7.2)

where \( n_1 \) and \( n_2 \) are calculated for the initial and feed state, respectively. From a physical point of view, this condition means that the desorption front of the initial state moves slower along the column than the adsorption front of the feed state. As a result, the non-classical delta-shock composition front develops and accumulates matter as it travels along the column. The speed of its propagation is given by [51]:

\[ t_{DS}^R = \frac{V}{Q} \left( \epsilon + (1 - \epsilon) \frac{H_1 K_2 n_2 + H_2 K_1 n_1}{H_1 K_2 c_2 + H_2 K_1 c_1} \right) \]  

(7.3)

where \( V \) and \( \epsilon \) are the column volume and its overall void fraction, and \( Q \) is the volumetric flow rate. Finally, it was further shown, that the mass present in the travelling spike increases linearly as it travels along the column [51], i.e. when comparing different column lengths one expects a stronger developed delta-shock for longer columns.
7.2.2 Detailed Simulations

Simulating the delta-shock is numerically difficult since very steep composition fronts are involved. As a result, the finite difference model (FDM) presented in chapter 3 cannot be applied for that purpose as the solver breaks down as soon as the concentrations are large enough to result in a delta-shock. However, Javeed et al. have recently presented a numerical method based on finite volume discretization that was shown to be applicable to simulate delta-shocks \[76\]. Therefore, this model was implemented in this work and thoroughly tested. In figure 7.1 the theoretical retention time of the delta-shock calculated from equilibrium theory is compared to numerical results obtained from the finite volume model (FVM). The peak maxima of both Phenetole (PNT) and 4-tert-Butylphenol (TBP) were identified as numerical delta-shock retention time and are given for both 5 and 200 discretization steps (fig. 7.1a). This analysis demonstrates that the peak maxima are converging for larger numbers of discretization steps as expected from theory and that they approach the theoretical value of the delta-shock retention time. However, also the finite volume model breaks down, if large concentrations and large numbers of discretization steps are applied, e.g. for 200 cells this happens above 35% of the maximum concentrations studied, being \(c_1 = 24.6 \text{ g/l}\) and \(c_2 = 90.90 \text{ g/l}\). Therefore, the experimentally relevant concentrations of \(c_1 = 24.6 \text{ g/l}\) and \(c_2 = 90.90 \text{ g/l}\) can only be simulated when maximum five discretization steps are used, which is clearly not enough for obtaining accurate results as illustrated in figure 7.1a. The latter is further illustrated in figure 7.1b where the effect of the discretization steps for fixed concentrations, namely 25% of the maximum values, is studied. Thus showing that an accurate description requires at least 200, better 400, discretization steps.

7.3 Experimental

7.3.1 Materials and methods

All experiments were carried out on a modular HPLC unit (Agilent Technologies 1200 Series, Palo Alto, CA, USA) equipped with a quaternary dual piston pump with an online degasser. Furthermore, the unit comprised an autosampler, a thermostated column compartment, a diode-array detector to monitor simultaneously a broad range of wavelength as well as a refractive index detector. Additionally, the unit was equipped with a manual 5 ml injection loop (Rheodyne 7725i, Rohnert Park, CA, USA) that was connected to the data acquisition software (Agilent ChemStation for LC 3D systems Rev. B.04.02 SP1 [208], Palo Alto, CA, USA) so as data acquisition was automatically started when the loop was manually switched to the injection position. All experiments were carried out at a fixed temperature of 23°C and volumetric flow rates \(Q\) ranging from 0.7 ml/min to 1.2 ml/min were examined, however in most experiments the flow rate equaled \(Q = 1.2\) ml/min.

Most experiments were carried out on the stationary phase Zorbax 300SB-C18 (Agilent Technologies, Palo Alto, CA, USA) which is a microparticulate column packing material
Figure 7.1: Influence of the number of cells used in the finite volume code on the accuracy of the results: (a) Fixed number of cells, varying concentrations; (b) Fixed concentration (25% of the maximum values), varying number of cells. The following parameters were used: $H_1=1.41$, $K_1=-0.033$ l/g, $H_2=2.15$, $K_2=0.031$ l/g, $L_{col} = 25$ cm, $D_{col} = 0.46$ cm, $\epsilon = 0.61$, and 500 theoretical plates. It is further noted that the concentration ratio was kept constant and that concentrations are indicated in terms of percentage of their maximum values, being $c_1 = 24.6$ g/l and $c_2 = 90.90$ g/l. Finally, the retention time is given in dimensionless form.
CHAPTER 7. EXCURSUS ON THE DELTA-SHOCK

with a particle size of 5 µm and an interparticle pore size of 300 Å that features a sterically protected octadecyl stationary phase chemically bonded to ultra-high-purity porous-silica microspheres. Prepacked stainless steel columns of varying lengths (50 mm x 4.6 mm, 150 mm x 4.6 mm and 250 mm x 4.6 mm) were used throughout this work. Additionally, one series of experiments was carried out on a Zorbax Extend-C18 (Agilent Technologies, Palo Alto, CA, USA) column (50 mm x 4.6 mm, 5 µm) which incorporates bidentate organosilane compounds chemically bonded on a silica support. Furthermore, this stationary phase material is double endcapped as compared to the Zorbax 300SB-C18 phase which is not endcapped. The overall porosity $\epsilon$ was determined by injecting a highly diluted solution of Uracil (purity >99%, Aldrich, Steinheim, Germany) which is considered to be unretained. With the exception of the 15 cm Zorbax 300SB-C18 column, each of the above mentioned columns had an overall porosity of $\epsilon = 0.61$ whereas the 15 cm column had a porosity of $\epsilon = 0.62$.

The mobile phase consisted of 63% Methanol and 37% deionized water (v/v) and was prepared by measuring the appropriate volumes gravimetrically using a precision balance (Mettler Toledo PM4600 DeltaRange, Greifensee, Switzerland), namely 498.96 g Methanol (LiChrosolv, Merck KGaA, Darmstadt, Germany) and 370.00 g water (Milli-Q Advantage A10, Merck Millipore, Billerica, MA, USA) yielded 1 L of mobile phase. Prior to use, either as a solvent for the feed solutions or as an eluent, the mobile phase was well mixed for at least 20 min with a magnetic stirrer bar.

All feed solutions used in the first part of this work were single-solute solution consisting of either Phenetole (purity >99.0%, TCI Deutschland GmbH, Eschborn, Germany) or 4-tert-Butylphenol (purity 99%, Aldrich, Steinheim, Germany) dissolved in the mobile phase. Since it was aimed at quantitatively describing chromatographic elution profiles in a highly non-linear regime, it is essential to keep very accurately track of the feed concentrations. Therefore the solute weights were measured using an analytical semi micro balance featuring a readability of 0.01 mg (Mettler Toledo AX205 DeltaRange, Greifensee, Switzerland) and the solvent volume was determined with the precision balance specified above. The feed concentrations were then calculated in terms of solute mass per solvent volume assuming a solvent density of $\rho = 0.891$ g/L that was determined by accurately weighting eight 25 ml (bulb pipette 25±0.04 ml, Ex 20°C, Silberbrand ETERNA, BRAND GMBH + CO KG, Wertheim, Germany) samples of the mobile phase and averaging the results.

4-tert-Butylphenol was used as delivered without further purification. Phenetole in contrast had to be purified since the impurities, although amounting to less than 1%, had a significant effect on the elution profile as will be shown in section 7.3.4. The purification was carried out by vacuum distillation using two 25 cm Vigreux columns covered with Aluminium foil in series and applying a heater temperature of $\sim 90^\circ$C and a pressure of $\sim 50$ mbar. Three distillations in series were performed discarding in each step the bottoms and roughly 5 ml of foreshot as well as feint.

In the second part of this work binary frontal analysis and displacement experiments were carried out, which required fraction collection and offline analysis of the collected fraction
as discussed in chapter 5. For that purpose an auto fraction collector (GILSON FC 203B, Middleton, WI, USA) was used and fractions were collected at an interval of 0.15 min. These fractions were then analyzed using the 25 cm Zorbax 300SB-C18 column as well as both the same mobile phase and HPLC unit mentioned above. In the analytical measurements a flow rate of 1 ml/min and an injection volume of 5 µL were applied. Besides that, the same analytical method was applied to determine the Phenetole purity after each distillation step.

7.3.2 Frontal analysis experiments with the pure components

The adsorption isotherms of the pure single components, i.e. 4-tert-Butylphenol (Phenetole) dissolved in the mobile phase, were determined by frontal analysis applying feed concentrations between 2.48 g/L (5.18 g/L) and 90.35 g/L (24.01 g/L). In this technique an initially clean column is completely saturated with a feed solution of precisely determined concentration. The adsorbed phase concentration can be calculated according to a mass balance across the adsorption front, i.e.

\[ n_i = \frac{c_i(V_{\text{eq}} - \epsilon V)}{1 - \epsilon V} \]  \hspace{1cm} (7.4)

where \( V_{\text{eq}} \) is the breakthrough volume of the feed solution that is given by

\[ V_{\text{eq}} = (t_{\text{BT},i} - t_\text{d})Q \] \hspace{1cm} (7.5)

where \( t_{\text{BT},i} \) is the breakthrough time of component \( i \) and \( t_\text{d} \) the dead time due to extra-column dead volume. It is worth noting that the breakthrough time \( t_{\text{BT},i} \) for a favorable isotherm corresponds ideally to the inflection point of the shock front. However, in order to ensure generality, it is good practice to determine its value by applying the so-called equal area method, i.e. the area below the breakthrough curve from \( t = 0 \) to \( t = t_{\text{BT},i} \) should equal the area below the horizontal line of the plateau value and the breakthrough curve from \( t = t_{\text{BT},i} \) to the time when the plateau is reached. In order to apply the equal area method, the breakthrough curves recorded in terms of UV absorbance versus time were converted into concentration profiles by applying the following calibration curve

\[ A_{\text{F},i} = \frac{a_{1,i}c_{\text{F},i}}{1 + b_{1,i}c_{\text{F},i}} + \frac{a_{2,i}c_{\text{F},i}}{1 + b_{2,i}c_{\text{F},i}} \] \hspace{1cm} (7.6)

where \( A_{\text{F},i} \) is the plateau value in terms of UV absorbance corresponding to the feed concentration \( c_{\text{F},i} \) of component \( i \) and \( a_{j,i}, b_{j,i} (j = 1, 2, i = \text{PNT,TBP}) \) are the calibration factors.

Since the equal area method given by equation (7.4) is based on the basic principle of mass conversation yielding the adsorbed phase concentration at equilibrium with a given mobile phase concentration, it can be applied to determine any kind of adsorption isotherm by fitting the data to an according isotherm model provided that the column is completely saturated with the feed solution. In this work the data was fitted to the
generalized Langmuir isotherm given in equation (7.1). Since it was ultimately aimed at accurately capturing the delta-shock front in binary interaction experiments, it was in the first place crucial that the classical shocks, i.e. the adsorption front (desorption front) of 4-tert-Butylphenol (Phenetole), were well captured. Applying the equal area method on the adsorption front guarantees this prerequisite for the Langmuirian component (TBP), but not necessarily for the Anti-Langmuirian component (PNT) since the desorption shock will not be accurately captured if the real adsorption isotherm does not strictly follow equation (7.1). In order to better describe the desorption behavior of Phenetole, one could therefore alternatively calculate the adsorbed phase concentration from the experimentally determined desorption shock velocity according to

\[ n_i = \frac{c_{F,i}}{\nu} \left( \frac{t_{R,\text{shock}} Q}{\epsilon V} - 1 \right) \]

(7.7)

where \( \nu = \frac{1}{1 + \epsilon} \) is the phase ratio and \( t_{R,\text{shock}} \) is the breakthrough time of the desorption shock adjusted for the injection and the dead time. With reference to equation (7.7) it is worth pointing out that (i) when using equation (7.7) the functional form of the isotherm according to equation (7.1) is a priori assumed whereas equation (7.4) does not require an assumption of the functional isotherm form to determine the adsorbed phase concentration; (ii) equations (7.4) and (7.1) yield exactly the same results if the adsorption isotherm fulfills strictly equation (7.1), and (iii) the breakthrough time of the shock \( t_{R,\text{shock}} \) should be calculated by following the equal area principle outlined above.

The breakthrough experiments were initially carried out using the 25 cm Zorbax 300SB-C18 column and the 5 ml manual injection loop applying a volumetric flow rate of 1.2 ml/min. In order to decrease the band broadening due to the sample loop, the temporary injection method proposed by Coq et al. [75] was applied, i.e. the injection loop was manually closed after 3:20 min which corresponds to an injection volume of 4 ml. This method yielded good results for the Langmuirian component (TBP) which are summarized in figure 7.2.

However, as can be seen in figure 7.5, the method was not suitable for the Anti-Langmuirian component (PNT) since the injection volume was too small to completely saturate the column at high feed concentrations. Therefore, another series of breakthrough experiments was performed using the same volumetric flow rate but the 5 cm Zorbax 300SB-C18 column and a larger injection volume, namely 30 ml. The latter could only be realized by switching the channels of the quaternary HPLC pump, i.e. the column was flushed for 5 min with pure mobile phase, then it was switched to feeding PNT solution for 25 min and finally the column was regenerated by switching back to the pure mobile phase channel. The corresponding results are summarized in figure 7.3.

With reference to figure 7.3 it is worth noting that the channel switching method leads to more extra-column dispersion as compared to the injection loop method, namely a significant tailing can be observed which would lead to ”wrong” results if \( t_{R,\text{shock}} \) was determined according to the equal area method. Therefore, the elution time corresponding to the half height of the shock front was taken instead to be applied in equation (7.7).
Figure 7.2: Frontal analysis on 4-tert-Butylphenol: (a) Breakthrough experiments (orange lines) in comparison to numerical simulations (blue lines); (b) Adsorption isotherm where the circles represents the experimental measurements determined from figure (a) and the solid line the corresponding Langmuir isotherm with $H_{\text{TBP}} = 2.15$ and $K_{\text{TBP}} = 0.031 \text{ L/g}$. (25 cm Zorbax 300SB-C18 column, $Q = 1.2 \text{ ml/min}$, $V_{\text{inj}} = 4 \text{ ml}$)
Figure 7.3: Frontal analysis on Phenetole: (a) Breakthrough experiments (orange lines) in comparison to numerical simulations (blue lines); (b) Adsorption isotherm where the circles (squares) were calculated from the shock velocity of the desorption step assuming an Anti-Langmuir isotherm (from a mass balance over the adsorption step) using the experimental profiles of figure (a). The solid line represents the Anti-Langmuir isotherm fitted to the values obtained by the shock velocity method resulting in $H_{\text{PNT}} = 1.41$ and $K_{\text{PNT}} = -0.033$ L/g. (5 cm Zorbax 300SB-C18 column, $Q = 1.2$ ml/min, $V_{\text{inj}} = 4$ ml)
With reference to figures 7.2b and 7.3b it is noted that the adsorbed phase concentration was determined by applying equation (7.4) for TBP and both equation (7.4) and equation (7.7) for PNT. The adsorption isotherms were fitted to the values obtained by equation (7.4) for TBP, respectively to those obtained by equation (7.7) for PNT. In both cases the extra-column dead time was accurately accounted for and was determined by injecting a tracer solution without installing a column. The corresponding dead times were 0.05 min (0.99 min) when using the manual injection loop (the channel switching method).

Finally it is worth commenting on the fact that two different column lengths were used to determine the single component isotherms of the two substances. It would be certainly desirable to perform this exercise on the same column, however on the one hand it is practically difficult to saturate a long column (25 cm) completely with the Anti-Langmuirian component when applying very high feed concentrations. Using a short column (5 cm) on the other hand for determining the adsorption isotherm of the Langmuirian component is hampered by the fact that the breakthrough times for different feed concentrations are very similar and therefore prone to error. Consequently, I am convinced that the PNT isotherm is best determined on the shortest column, whereas the TBP isotherm is best determined on the longest column.

7.3.3 Reproducing the ”delta-shock” experiment

The classical delta-shock experiment as described previously\,[51, 52]\ occurs when a column initially saturated with Phenetole experiences a step change at the inlet from PNT solution to TBP solution. In practice such an experiment is carried out by using the different channels of the quaternary HPLC pump. Namely, the column is equilibrated for a time $t_{eq}$ and it is switched for a time $t_{PNT}$ to the channel containing the PNT solution, afterwards the TBP solution is applied for a time $t_{TBP}$ before the column is regenerated with pure mobile phase for a time $t_{reg}$. This classical delta-shock experiment is illustrated in figure 7.4 and compared to the elution profiles without interaction, i.e. the case where pure mobile phase is applied during time interval $t_{TBP}$ ($t_{PNT}$) instead of TBP (PNT) solution. Besides demonstrating the experimental procedures, figure 7.4 also illustrates that the material accumulated in the delta-shock corresponds to the material being present in the overlapping part of the two non-interacting profiles.

Besides the classical experiment where the interaction of PNT and TBP occurs immediately after the step change at the inlet of the column, this work studied also a new type of experiment in which the sequence $t_{eq} \rightarrow t_{PNT} \rightarrow t_{TBP} \rightarrow t_{reg}$ is modified to a situation where pure mobile phase is applied between the PNT solution and the TBP solution for a time $t_{int}$, i.e. $t_{eq} \rightarrow t_{PNT} \rightarrow t_{int} \rightarrow t_{TBP} \rightarrow t_{reg}$. By doing so, two classical shocks are created, that later merge into a delta-shock if $t_{int}$ is short enough or the column is long enough so as the adsorption shock of TBP can overtake the desorption front of PNT. This type of experiment is particularly interesting to demonstrate the increasing strength of the delta-shock depending on the path length it covers.
Figure 7.4: Illustration of the classical delta-shock experiment (orange line) where the column was first equilibrated for 5 min with pure mobile phase. It was then saturated for 35 min with a 24.0 g/L Phenetole solution which was displaced by a 90.0 g/L 4-tert-Butylphenol solution. After another 35 min the column was regenerated by feeding pure mobile phase. The blue (green) line represents an analogous sequence of inlet step changes, however the 4-tert-Butylphenol solution (Phenetole solution) was replaced by pure mobile phase. The figure nicely illustrates, that the material being present in the overlapping part of the blue and green curves, accumulate within a spike when the substances are interacting. (25 cm Zorbax 300SB-C18 column, \(Q = 1.2\) ml/min, \(c_{\text{PNT}} = 24.0\) g/L, \(c_{\text{TBP}} = 90.0\) g/L)
7.3.4 Practicalities

Since this work deals with very high feed concentrations in a highly non-linear chromatographic regime a number of practically relevant aspects have to be further discussed. It was already pointed out that the feed solutions have to be prepared carefully, especially in the case of Phenetole relatively small errors in the feed concentration would considerably shift the position of the shock front. Furthermore, the presence of impurities causes heavily distorted elution profiles and the volumetric flow rate plays a role which is not yet fully understood. The latter two aspects are discussed in greater detail in the following subsections.

Influence of impurities

As briefly mentioned in section 7.3.1 Phenetole was purified by distillation prior to use. The purification is visualized by the analytical chromatogram given in figure 7.5a recorded at 200 nm where the detector is saturated for the Phenetole peak, however that wavelength is well suited to illustrate that at least five impurities, one being less and four being more retained than Phenetole, are present in the crude material. Furthermore, figure 7.5a demonstrates that the purification method consisting of three distillations is effective in reducing the impurities.

Initially, this work employed unpurified Phenetole as reported previously [52]. However, when aiming at determining the adsorption isotherm by frontal analysis, messy elution profiles as shown in figure 7.5b were obtained. Given the fact that the impurities amount according to the manufacturer to less than one weight percent, these results were rather surprising, but it was clear that only a repetition of the experiments using purified Phenetole can deliver accurate isotherm parameters. Since the first distillation was rather effective in removing the impurities, the breakthrough experiments were repeated using that material and the elution profiles obtained are shown in figure 7.5c. Note that in both cases the 25 cm Zorbax 300SB-C18 column was used, but that figures 7.5b and 7.5c are not quantitatively comparable since different flow rates and injection volumes were applied. Although much better results are achieved with the distilled Phenetole, figure 7.5c shows that both further purification as well as a larger injection volume and/or a short column are necessary for accurate isotherm determination. Therefore, two further distillation steps were performed and another, finally successful, series of breakthrough experiments was performed on the 5 cm Zorbax 300SB-C18 column (see fig. 7.3a).

The striking influence of the impurities on the single component measurements suggested to double-check whether they are also affecting the delta-shock phenomenon. Therefore, two identical classical delta-shock experiments were performed, however once using unpurified and once using 1x distilled Phenetole. The resulting elution profiles reported in figure 7.5d show that although equal feed concentrations were applied, the Phenetole plateau before the occurrence of the de delta-shock has a significantly higher UV absorbance which is a result of the strongly light absorbing impurities. More importantly, the figure further shows that the peak believed to be the delta-shock is unaffected by the


Figure 7.5: Influence of impurities on the determination of the Phenetole adsorption isotherm: (a) Analytical injections of the unpurified and distilled Phenetole solutions; (b) Frontal analysis using unpurified Phenetole (25 cm Zorbax 300SB-C18 column, $Q = 0.8$ ml/min, $V_{inj} = 5$ ml); (c) Frontal analysis using 1x distilled Phenetole (25 cm Zorbax 300SB-C18 column, $Q = 1.2$ ml/min, $V_{inj} = 4$ ml); (d) Delta-shock experiments using unpurified and 1x distilled Phenetole (5 cm Zorbax 300SB-C18 column, $Q = 0.7$ ml/min, $c_{PNT} = 20.0$ g/L, $c_{TBP} = 75.0$ g/L)
Figure 7.6: Phase separation across the travelling spike. Sample 13 was collected just before the spike, whereas the milky solution of sample 14 was collected right at the beginning of the relatively broad spike.

presence of impurities. Nonetheless, 3x distilled Phenetole was employed throughout the remaining part of this work.

Liquid-liquid phase separation and the effect of the flow rate

In the previous publication on the system studied in this work, reproducibility issues concerning the UV signal across the delta-shock were reported [52]. In this context, it is worth adding that the UV signal both in the previous work [52] as well as in the present work was completely saturated over the whole spectrum at the elution time of the spike, provided that the latter was "fully developed". The terminology "fully developed delta-shock" was previously used to distinguish between experiments yielding well-defined peaks to those yielding poorly reproducible distorted peak shapes or experiments yielding no peak at all due to lower concentrations. The fact, that "fully developed delta-shocks" result in saturation of the UV signal over the whole spectrum was previously rationalized through the theoretically unbound concentrations being present in the traveling spike. Newer findings suggest that this interpretation was wrong; first of all it is not plausible why the detector should be saturated at wavelengths where both substances are not UV-active. Secondly, fraction collection across the traveling spike has revealed that the chromatographic interaction results in concentrations above the solubility limit, i.e. liquid-liquid phase separation occurs. As a result, a milky solution is leaving the column during the timespan of the spike, which of course absorbs all incoming light over the whole spectrum and explains the observation in a more convincing manner. The liquid-liquid phase separation is also illustrated in figure 7.6.

The observation of phase separation brings us back to the issue concerning poorly reproducible distorted peak shapes that occurred only at feed concentrations that were
expected to yield a delta-shock. Previously, these reproducibility issues were attributed to rapid degradation of Phenetole dissolved in the mobile phase [52]. However, no degradation products were detectable which was rather weakly explained by claiming co-elution of the degradation products with Phenetole [52]. Meanwhile, it is believed that degradation of Phenetole is not an issue, since a series of experiments that was repeated, after the solutions were simply stored at room temperature for 16 days, demonstrated that no significant differences in the resulting elution profiles could be observed. However, the poorly reproducible distorted peak shapes were also obtained at the beginning of the present work as can be seen in figure 7.7, which shows a series of experiments on the 25 cm Zorbax 300SB-C18 column applying the sequence $t_{eq} = 5 \text{ min} \rightarrow t_{PNT} = 15 \text{ min} \rightarrow t_{TBP} = 15 \text{ min} \rightarrow t_{reg} = 25 \text{ min}$ and feed concentrations of 20 g/L and 75 g/L for PNT and TBP, respectively. It can be seen that a ”fully developed” peak is obtained at a volumetric flow rate of 1.2 ml/min, whereas distorted peaks are obtained at $Q = 1.0 \text{ ml/min}$ and $Q = 0.7 \text{ ml/min}$. The same series of experiments was performed on the 5 cm column (not shown here) where no flow rate effect could be observed, i.e. a ”fully developed” peak was obtained at all three flow rates. After this observation, all further experiments were carried out using a fixed flow rate of 1.2 ml/min and no further irregular distorted peak shapes were observed onwards.

Under the given flow regime, one would of course expect an increase in band broadening with increasing flow rates. The opposite behavior illustrated in figure 7.4 is not yet understood, but it is believed that the formation of a biphasic mixture hampers the

Figure 7.7: Effect of the flow rate on the development of a fully developed spike. (25 cm Zorbax 300SB-C18 column, $c_{PNT} = 24.0 \text{ g/L}$, $c_{TBP} = 90.0 \text{ g/L}$)
application of classical chromatographic concepts, i.e. the classical mechanisms for band broadening do most likely no longer apply. In this case, the ratio of the residence time to the characteristic time for axial spreading of the biphasic solution is apparently the determining factor for band broadening. Considering that no flow rate effect was observed in the 5 cm column substantiates this hypothesis further, since the shorter column features not only a shorter residence time but also a smaller fraction of biphasic solution due to the shorter pathway of the traveling spike.

7.4 Results

In this section four series of interaction experiments carried out on the stationary phase Zorbax 300SB-C18 are presented. Using the single component isotherm parameters derived in section 7.3.2 and combining them to a binary M2-isotherm allows for comparison with equilibrium theory. However, a comparison to numerical simulations is not possible since the feed concentrations studied are too high, which leads to a breakdown of the solver as discussed in section 7.2.2. Additionally, binary breakthrough and displacement experiments are presented in section 7.4.2. Finally, a number of experiments carried out on Zorbax Extend-C18 (section 7.4.3) is presented. This stationary phase does not only exhibit similar features as Zorbax 300SB-C18 during binary interaction, but shows also a peculiar single component behavior in the case of Phenetole.

7.4.1 Reproduction of the "delta-shock" experiments

A variety of interaction experiments following the general sequence \( t_{\text{eq}} \rightarrow t_{\text{PNT}} \rightarrow t_{\text{int}} \rightarrow t_{\text{TBP}} \rightarrow t_{\text{reg}} \) with \( t_{\text{eq}} = 5 \text{ min}, t_{\text{PNT}} = t_{\text{TBP}} = t_{\text{reg}} = 25 \text{ min}, Q = 1.2 \text{ ml/min} \) and varying values of \( t_{\text{int}}, c_{\text{PNT}} \) and \( c_{\text{TBP}} \) was performed on each of the three Zorbax 300SB-C18 columns. The experimental conditions and the resulting residence time of the traveling spike, if applicable, are given in table 7.1 which furthermore lists the corresponding values from equilibrium theory assuming an M2 isotherm and using the parameters given in figures 7.2 and 7.3.

Experiments with same injection time, different feed concentrations

A first series of experiments was carried out on the 5 cm column with \( t_{\text{int}} = 10 \text{ min} \) and varying feed concentrations keeping the ratio of \( c_{\text{PNT}} \) and \( c_{\text{TBP}} \) constant (see figure 7.8a). These experiments were first of all intended to determine the Phenetole isotherm and in fact, the concentration profile shown in figure 7.3a were directly derived from the first part of the elution profile shown in figure 7.8a. Additionally, these experiments served as a means to cross-check whether the single component isotherm parameters of TBP, which were determined on the 25 cm column, are also valid on the shorter column which was packed with a different batch of the same stationary phase material. With reference to the inset plots of 7.8a providing a zoom onto the classical shock fronts of both components
it is noted that the numerical simulation satisfactorily captures the adsorption front of TBP, even though its isotherm parameters were determined only on the 25 cm. The good agreement on the desorption front of Phenetole is obvious when recalling figure 7.3. After having proven that the single component isotherm parameters of both substances are valid under conditions where no interaction of PNT and TBP takes place, the series was repeated keeping all experimental conditions despite \( t_{\text{int}} \) constant. By setting \( t_{\text{int}} = 0 \) conditions were created that lead to immediate interaction of the two components at the column inlet. Therefore, a delta-shock should form immediately after switching from PNT to TBP if the M2 isotherm could indeed describe the binary system. Given that even the lowest feed concentration applied in this series was above the theoretical threshold for the occurrence of a delta-shock, one would expect to observe a spike in each experiment. However, the experimental results given in figure 7.8 show that a spike is only formed for the highest feed concentration whereas the lowest feed concentration does not show any sign of a peak. In between those extremes, noticeable shoulders of increasing width can be seen. It is worth noting that similar results were obtained in the previous work [52] where this was attributed to dispersion. In this thesis a different interpretation is proposed, i.e. the results in figure 7.8 should be regarded as a first evidence towards overthrowing the assumption that the binary system of PNT and TBP can indeed be described by a simple M2 isotherm.

Experiments with varying injection times

An additional series of experiments at constant feed concentration and constant feed flow rate but varying \( t_{\text{int}} \) was performed on both the 15 cm and the 25 cm column, the corresponding experimental elution profiles being shown in figures 7.9 and 7.10 respectively. At \( t_{\text{int}} = 10 \text{ min} \) the distance between the adsorption front of TBP and the desorption front of PNT is large enough to prevent interaction on either of the two columns, i.e. the traveling path is on either column not long enough for TBP to overtake PNT. This expectation from the single component isotherm parameters, is indeed observed on both columns and allows for assessing the validity of the latter for the respective column. For these non-interacting conditions figure 7.9 shows relatively good agreement of experiment and simulation with reference to the position of both classical shocks, whereas in figure 7.10 only the position of the TBP adsorption shock is well captured whilst the experimental PNT desorption front is significantly faster than the simulated one. With reference to table 7.1 it is noted that if the M2 isotherm was correct, one would expect a spike for the 25 cm column for \( t_{\text{int}} = 7 \text{ min} \), whereas no spike should be observed on the 15 cm column. However, on both columns these conditions do not result in a spike, which is attributed to the fact that the PNT desorption shock on the 25 cm column moves faster than expected. Decreasing \( t_{\text{int}} \) further to 3 min, 1.5 min and 0 min leads to the formation of a traveling spike in each case and on both columns which is in agreement with the prediction from equilibrium theory.

It is further noted that the binary interaction occurs closer and closer to the column inlet as the duration of \( t_{\text{int}} \) decreases, i.e. the traveling spike covers a longer path and can thus
Figure 7.8: Effect of feed concentration (feed concentrations reported in table 7.1): (a) Experimental (orange) and numerically simulated (blue) elution profiles for the sequence 5 min MP - 25 min PNT - 10 min MP - 25 min TBP - 25 min MP using different feed concentrations. The inset plots demonstrate that the position of both shock fronts are well captured by the model. (b) Ditto, however without feeding MP between the PNT and TBP solutions. Here, the inset plot represents a zoom on the spike. (5 cm Zorbax 300SB-C18 column, $Q = 1.2$ ml/min)
Figure 7.9: Effect of interaction time: Experimental (orange) and numerically simulated (blue) elution profiles for the sequence 5 min MP - 25 min PNT - $t_{\text{int}}$ min MP ($t_{\text{int}} = 0, 1.5, 3.0, 7.0, 10.0$) - 25 min TBP - 25 min MP. The inset plot represents a zoom on the relevant shock fronts. (15 cm Zorbax 300SB-C18 column, $Q = 1.2$ ml/min, $c_{\text{PNT}} = 24.6$ g/L, $c_{\text{TBP}} = 90.9$ g/L)
Figure 7.10: Effect of interaction time: Experimental (orange) and numerically simulated (blue) elution profiles for the sequence 5 min MP - 25 min PNT - \( t_{\text{int}} \) min MP (\( t_{\text{int}} = 0, 1.5, 3.0, 7.0, 10.0 \)) - 25 min TBP - 25 min MP. The inset plot represents a zoom on the relevant shock fronts. (25 cm Zorbax 300SB-C18 column, \( Q = 1.2 \) ml/min, \( c_{\text{PNT}} = 24.6 \) g/L, \( c_{\text{TBP}} = 90.9 \) g/L)
accumulate more material. As a result, the spike should get steeper and steeper, whereas the experimental profiles show that the spike gets wider as $t_{\text{int}}$ decreases, more specifically it covers almost one column volume in the extreme case. It is worth noting that the UV profiles lose its quantitative information during the timespan of the spike due to signal saturation as described above. Therefore, the increasing width could be regarded as a qualitative confirmation of the accumulation of matter as predicted by theory. However, one could also interpret it as an intermediate state instead of as a huge spike, which would be further evidence for doubting the existence of an experimental delta-shock.

Varying the interaction time is one way to assess whether the spike is indeed growing as it travels along the column. An alternative way is to look at the elution profiles for different column lengths as discussed next.

**Experiments with same injection time, different column lengths**

Experimentally, there is no means to observe how the spike is growing as it travels along a column. However, by using columns of different length and recording their outlet profiles, one can at least take snapshots at discrete instances in time and space. This exercise can depict the accumulation actually happening in a long column only if the conditions in the shorter ones are exactly identical to those prevailing in the longest column. However, as discussed in the previous sections, neither the void fraction nor the isotherm parameters of the three columns are fully identical, moreover the highest feed concentration applied in the 5 cm column is close, but not equal to the one applied in the 15 cm and 25 cm column. Nonetheless, figure 7.11 is well suited to at least qualitatively describe the effect of column length, respectively traveling distance, for a case without interaction ($t_{\text{int}} = 10$ min) and the case with the highest degree of interaction, i.e. $t_{\text{int}} = 0$ min. For the latter case, the peak gets wider as the column length increases, which is in agreement with the previous section and allows for the same interpretations mentioned above.

**Comparison with equilibrium theory**

The last two columns of table 7.1 provide the elution times of the traveling spike, if applicable, observed experimentally and evaluated in the center of the spike, as well as those calculated using the equilibrium theory solution. Furthermore, all experiments that exhibited a spike are comprehensively summarized in figure 7.12. These results, conclusively demonstrate that (i) the spike gets wider the longer the binary interaction is, (ii) the spike moves in good agreement with a linear velocity along the column, and (iii) there are significant discrepancies between experiments and theory, especially for cases where the timespan of the binary interaction is large. These findings were the last piece of evidence suggesting that the current system cannot be described through a simple M2 isotherm and thus motivated a further investigation of the binary interaction by performing binary breakthrough and displacement experiments as discussed next.
Figure 7.11: Effect of column length: Selected experimental profiles of figures 7.8 to 7.10 for (a) the case with no interaction, i.e. $t_{\text{int}} = 10$ min and (b) the case with immediate interaction, i.e. $t_{\text{int}} = 0$ min. The solid black lines in the physical plane illustrate the shock velocities according to equilibrium theory.
Table 7.1: Summary of all experiments carried on the stationary phase Zorbax 300SB-C18 applying a volumetric feed flow rate of 1.2 ml/min and the sequence $t_{\text{eq}} \rightarrow t_{\text{PNT}} \rightarrow t_{\text{int}} \rightarrow t_{\text{TBP}} \rightarrow t_{\text{reg}}$ with $t_{\text{eq}} = 5$ min, $t_{\text{PNT}} = t_{\text{TBP}} = t_{\text{reg}} = 25$ min and $t_{\text{int}}$ according to the values given in column 2. The elution time of the experimental delta shocks is compared to the equilibrium theory solution. In all cases the extra-column dead time of 0.99 min is included.
Figure 7.12: Comparison of experimental and theoretical retention time of the spike: (a) Summary of all experiments where an experimental spike was observed, (b) Retention time of the spike versus column length for \( t_{\text{int}} = 0 \) min. Note that the retention times were corrected for dead time and equilibration times for better comparison. Furthermore, the width of the experimental spike is indicated with a solid blue line.
7.4.2 Binary breakthrough and displacement experiments

An extensive series of binary breakthrough experiments was performed studying different concentrations as well as different ratios of the PNT and TBP concentrations. More specifically the ratio \( c_{\text{PNT}} : c_{\text{TBP}} \) was varied from 1:3 (fig. 7.13), to 1:1 (fig. 7.14), and 3:1 (fig. 7.15). The resulting elution profiles for a \( c_{\text{PNT}} : c_{\text{TBP}} \) ratio of 1:3 were quite surprising since the breakthrough of TBP occurred always before the breakthrough of PNT. For the other two concentration ratios the breakthrough of the two components occurred almost simultaneously. Only when the concentrations were decreased into the nearly linear range, PNT eluted before TBP (fig. 7.15a) as one would expect if the system was following an M2 isotherm.

Furthermore, a series of binary displacement experiments demonstrated that the interaction of PNT with TBP changes from competitive to cooperative as the concentration increases (figs. 7.16a to 7.16c). In addition, all displacement experiments showed rather broad interaction zones instead of a spike that would be expected if the simple M2 isotherm resulting from combining the single component parameters was able to describe the system. Therefore, it is concluded that the PNT-TBP system is definitely not subject to an M2 isotherm and can thus not lead to formation of delta-shocks as previously claimed \[52\]. This thesis proposes instead a generalized Bi-Langmuir isotherm, i.e.

\[
n_i = \frac{H_{a,i}c_i}{1 + K_{a,i}c_1 + K_{a,2}c_2} + \frac{H_{b,i}c_i}{1 + K_{b,i}c_1 + K_{b,2}c_2}
\]

(i = 1, 2) (7.8)

where the parameters \( K_{a,i} \) and \( K_{b,i} \) can have positive or negative values.

Recently, an equilibrium theory solution for a generalized Langmuir isotherm of the type L-M1, i.e. \( H_{a,1} < H_{a,2}, H_{b,1} > H_{b,2} \), positive values for \( K_{a,1}, K_{a,2}, K_{b,2} \), and a negative value for \( K_{b,1} \), was developed \[78, 79\]. The explanation of the latter goes beyond the scope of this chapter, however, the equilibrium theory solution could be used to fit the eight parameters of the generalized Bi-Langmuir isotherm to the experimental elution profile shown in figures 7.13 to 7.17. The resulting parameters are given in table 7.2 and were used to simulate the elution profiles using the finite volume model with \( 10^6 \) theoretical plates. The agreement between experiments and model is good for almost all breakthrough experiments as well as for the displacement experiments at moderate feed concentrations. At high feed concentrations the model fails in describing the displacement experiments (see figure 7.17), which is well rationalized for the conditions reported in

<table>
<thead>
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<th>Bi-Langmuir Isotherm</th>
<th>PNT</th>
<th>TBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>( H_{a,i} ) [-]</td>
<td>0.033</td>
<td>2.268</td>
</tr>
<tr>
<td>( K_{a,i} ) [L/g]</td>
<td>0.028</td>
<td>0.052</td>
</tr>
<tr>
<td>( H_{b,i} ) [-]</td>
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</tr>
<tr>
<td>( K_{b,i} ) [L/g]</td>
<td>-0.022</td>
<td>0.012</td>
</tr>
</tbody>
</table>

Table 7.2: Parameters of a generalized Bi-Langmuir isotherm fitted to binary breakthrough and displacement experiments.
figure 7.17c where liquid-liquid phase separation occurred, which is not accounted for in the model. However, the discrepancies in figures 7.17a to 7.17b are not understood since no liquid-liquid phase separation occurs under these conditions.
Figure 7.13: Binary frontal analysis experiments using a concentration ratio PNT:TBP of 1:3 and increasing concentrations from (a) to (f) as indicated. The experiments were repeated at least twice and the repetitions are indicated as exp(2) and exp(3) for the first and the second repetition, respectively. Red symbols stands for the more retained component TBP, whereas blue symbols denote PNT. Moreover, the solid black lines denote the solution of the numerical simulation using the generalized Bi-Langmuir isotherm, whose parameters are given in Table 7.2.
Figure 7.14: Binary frontal analysis experiments using a concentration ratio PNT:TBP of 1:1 and increasing concentrations from (a) to (c) as indicated. The same notation as in 7.13 applies.
Figure 7.15: Binary frontal analysis experiments using a concentration ratio PNT:TBP of 3:1 and increasing concentrations from (a) to (d) as indicated. The same notation as in 7.13 applies.
Figure 7.16: Binary displacement experiments where the column was initially saturated with: (a)-(c) a 12 g/l PNT solution that was displaced by a TBP solution having a concentration of 20 g/l (fig. (a)), 40 g/l (fig. (b)), and 80 g/l (fig. (c)). In (d)-(f) the same sequence was performed, however at an initial PNT concentration of 18 g/l. The same notation as in 7.13 applies.
Figure 7.17: Binary displacement experiments where the column was initially saturated with a 24 g/l PNT solution that was displaced by a TBP solution having a concentration of 20 g/l (fig. (a)), 40 g/l (fig. (b)), and 80 g/l (fig. (c)). The same notation as in 7.13 applies.
7.4.3 The Zorbax Extend-C18 stationary phase

In the previous work, the 5 cm Zorbax Extend-C18 column was reported to not exhibit fully developed spikes [52]. This claim was also tested in this work and the opposite was found as shown in figure 7.18, where a “classical delta-shock experiment” is presented. More specifically, the procedure applied above on Zorbax 300SB-C18 column was carried out with \( t_{\text{int}} = 0 \) min which resulted in a well defined peak (the same was analogously observed for values of 1.5 min and 3 min, but is not shown here). Furthermore, the figure shows a peculiar adsorption behavior of PNT under non-interacting conditions, i.e. when \( t_{\text{int}} = 10 \) min. As on the Zorbax 300SB-C18 column, the adsorption is initially subject to a simple wave transition that turns at \( t \approx 12 \) min into a shock transition towards a flat plateau. The desorption in contrast is no longer a pure shock transition, but also combination of simple wave and shock, i.e. a semi-shock transition. Such a behavior is possibly due to a type V adsorption isotherm, however, the author is not aware of any system in liquid chromatography that is subject to such an isotherm.

In order to substantiate the type V isotherm hypothesis single component breakthrough experiments applying the same technique as used for the TBP isotherm determination were performed. The resulting elution profiles (see figure 7.18), particularly the one with the high feed concentration, qualitatively confirm the observations and the hypothesis outlined above. The data does, however, not allow to draw quantitative conclusions on the isotherm, as this would require both larger injection volumes so as to completely saturate the column and higher feed concentrations. The latter is hampered by the limited miscibility of Phenetole in the mobile phase. Therefore, no further experimentally effort was put in better characterizing this system.

Figure 7.18: Peculiar adsorption behavior of Phenetole observed on a 5 cm Zorbax Extend-C18 column: Both the frontal analysis shown in figure (a) as well as the binary experiments shown in figure (b) suggest a type V isotherm.
CHAPTER 7. EXCURSUS ON THE DELTA-SHOCK

7.5 Conclusions

This chapter studied the Phenetole - 4-tert-Butylphenol system in Methanol/Water that was previously claimed to be subject to an M2 isotherm and thus to result in the occurrence of delta-shocks [52]. It was convincingly demonstrated that this interpretation has to be overthrown and that the system behaves in a much more complex manner that could be relatively well described through the introduction of a generalized Bi-Langmuir isotherm of the L-M1 type. Moreover, it was shown that the chromatographic interaction leads to intermediates states, whose concentrations are above the solubility limit. This results in liquid-liquid phase separation, that was identified as the cause for saturating the UV profile at all wavelengths. This phenomenon was previously interpreted as the "fingerprint of the delta-shock" demonstrating very high concentrations [52].

The findings of this work do not only prove the previous interpretations wrong, but also rise a couple of new questions, which can be the subject of a future work. The most important open question resides in the liquid-liquid phase separation that leads to unusual elution profiles, which are not yet understood. A future work should address this issue by examining what happens in the pores and the voids of a chromatographic column when liquid-liquid phase separation occurs. Furthermore, it would be interesting to address the numerical difficulties encountered when delta-shocks at high feed concentration are simulated. Finally, the explanation of the peculiar single component behavior of PNT on Zorbax Extend-C18 would be another interesting research topic.

7.6 Nomenclature

\[ A_{F,i} \] UV plateau value corresponding to \( c_{F,i} \) [mAU]
\[ a_{j,i} \] UV calibration factors [mAU l g\(^{-1}\)]
\[ b_{j,i} \] UV calibration factors [l g\(^{-1}\)]
\[ c_{F,i} \] Feed concentration of component \( i \) [g l\(^{-1}\)]
\[ c_i \] Concentration of component \( i \) [g l\(^{-1}\)]
\[ D_{col} \] Column Diameter [cm]
\[ H_{a,i} \] Parameters in Bi-Langmuir isotherm [-]
\[ H_{b,i} \] Parameters in Bi-Langmuir isotherm [-]
\[ H_i \] Henry’s constant of component \( i \) [-]
\[ K_{a,i} \] Parameters in Bi-Langmuir isotherm [l g\(^{-1}\)]
\[ K_{b,i} \] Parameters in Bi-Langmuir isotherm [l g\(^{-1}\)]
\[ K_i \] Equilibrium constant of component \( i \) [l g\(^{-1}\)] [-]
\[ L_{col} \] Column length [cm]
\[ n_i \] Adsorbed phase concentration [g l\(^{-1}\)]
\[ Q \] Volumetric flow rate [ml min\(^{-1}\)]
\[ t_{BT,i} \] Breakthrough time of component \( i \) [min]
\[ t_d \] Dead time [min]
\[ t_{eq} \] Duration of equilibration with pure solvent [min]
\( t_{\text{int}} \) Timespan during which pure solvent is fed to partly displace PNT [min]
\( t_{\text{PNT}} \) Duration of equilibration with PNT solution [min]
\( t_{\text{R,shock}} \) Breakthrough time of a classical shock [min]
\( t_{\text{DS}} \) Breakthrough time of a delta-shock [min]
\( t_{\text{reg}} \) Duration of regeneration [min]
\( t_{\text{TBP}} \) Duration of equilibration with TBP solution [min]
\( V \) Column volume [ml]
\( V_{\text{eq}} \) Breakthrough volume in equal area method [ml]

Greek Letters
\( \epsilon \) Overall void fraction [-]
\( \nu \) Phase ratio [-]

Subscripts and Superscripts
ET Equilibrium theory
exp Experimental
\( i \) Component index \((i=\text{PNT,TBP})\)
\( j \) Index in UV calibration curve \((j=1,2)\)
\( \text{PNT} \) Phenetole
\( \text{TBP} \) 4-\textit{tert}-Butylphenol
A.1 Extra-column dead volume in the 3W-ISMB unit

In section 2.2.3 the effect of extra-column dead volume in small-scale 3W-ISMB units is discussed and it is stated that the process can become infeasible when extra-column dead volume effects are strictly taken into account. In section A.1.1 this claim is substantiated. Furthermore section A.1.2 presents a less stringent approach that accounts for the dead volume by only introducing effective flow rate ratios (see equation (2.21)) without changing the structure of the ideal case (see equations (2.13a) to (2.13f)).

A.1.1 Strict Constraints

In order to prevent break through of component C in column 2 and to account for the increased residence time due to extra-column tubing the following constraints are necessary:

\[ m_3 - m_1^D \leq \tilde{H}_A \]  
\[ \tilde{H}_A \leq m_4 - m_1^D \]  
\[ m_3 + m_4 - m_1^D \leq \tilde{H}_B \]  
\[ \tilde{H}_B \leq m_2 + m_4 - m_1^D \]  
\[ m_2 + m_3 + 2m_4 - m_2^D \leq \tilde{H}_C \]  
\[ \tilde{H}_C \leq m_1 + m_2 + 2m_4 - m_2^D \]
where $m_1^D$ and $m_2^D$ are given in equations (2.22a) and (2.22b). It is worth pointing out that a distinction of cases in equation (A.1f) is no longer necessary due to equation (A.1e) which in fact means, that the most retained component (C) has to be trapped in the column and carried backwards with the simulated movement of the solid until it reaches column 1, i.e. a condition similar to 3S-ISMB. It is therefore to be expected that the adoption of equation (A.1e) may also render the 3W-ISMB process infeasible for certain low-selectivity systems.

With reference to equations (A.1a) to (A.1f) the dimensionless flow rate ratios $m_j$ are transformed in order to obtain simple relationships in the combined flow rate ratios $\hat{m}_j$ as above. For 3W-ISMB with non-negligible extra-column dead volume $\hat{m}_j$ is therefore defined as

$$\hat{m}_1 \equiv m_1 + m_2 + 2m_4 - m_2^D$$
$$\hat{m}_2 \equiv m_2 + m_4 - m_1^D$$
$$\hat{m}_3 \equiv m_2 + m_3 + 2m_4 - m_2^D$$
$$\hat{m}_4 \equiv m_4 - m_1^D \equiv \frac{\tilde{H}_A}{\varphi}$$

and end up with a new set of constraints that reads

$$\hat{m}_3 - \hat{m}_2 - \hat{m}_4 - 3m_1^D + m_2^D \leq \tilde{H}_A$$
$$\tilde{H}_A \leq \hat{m}_4$$
$$\hat{m}_3 - \hat{m}_2 - 2m_1^D + m_2^D \leq \tilde{H}_B$$
$$\tilde{H}_B \leq \hat{m}_2$$
$$\hat{m}_3 \leq \tilde{H}_C$$
$$\tilde{H}_C \leq \hat{m}_1$$

As for the case with negligible extra-column dead volume a right triangle in the $(\hat{m}_2, \hat{m}_3)$ plane defined by equations (A.3d) and (A.3e) is obtained, whereas equations (A.3a) and (A.3c) define a critical line below which complete ternary separation is feasible. This critical line is given by

$$\hat{m}_3 \leq \hat{m}_2 + \min \left( \frac{1}{\varphi} \right) \frac{\tilde{H}_A + 3m_1^D - m_2^D, \tilde{H}_B + 2m_1^D - m_2^D}$$

From the definition of $\hat{m}_2$ and $\hat{m}_3$ given in equations (A.2b) and (A.2c), respectively, it is evident that the line corresponding to a zero feed flow rate is not the diagonal as usual but a straight line parallel to the diagonal given by
\[ \dot{m}_3 = \dot{m}_2 + \frac{\tilde{H}_A}{\varphi} + 2m_1^D - m_2^D \]  

(A.5)

Consequently 3W-ISMB with non-negligible extra-column dead volume becomes infeasible when the band between the zero-feed-line (see equation (A.5)) and the critical line (see equation (A.4)) does not cross the triangular region of complete separation (see equations (A.3d) and (A.3c)), which occurs when \( \tilde{H}_C - \tilde{H}_B < \frac{\tilde{H}_A}{\varphi} + 2m_1^D - m_2^D \).

### A.1.2 Effective flow rate ratios

For the ternary system studied in section 2.3, the strict consideration of the extra-column dead volume as outlined above, renders the process infeasible. Therefore an alternative approach is applied that explicitly considers the increased residence time due to extra-column tubing, but neglects the effect of stagnant flow in some parts of tubing, i.e. the stringent constraint on the front of C (see equation (A.1e)) is relaxed and component C is allowed to break through column 2. The full set of constraints thus reads as:

\[
\begin{align*}
    m_3 - m_1^D &\leq \tilde{H}_A \\ 
    \tilde{H}_A &\leq m_4 - m_1^D \\
    m_3 + m_4 - m_1^D &\leq \tilde{H}_B \\
    \tilde{H}_B &\leq m_2 + m_4 - m_1^D \\
    m_2 + m_3 + m_4 - m_2^D &\leq \tilde{H}_C \\
    \tilde{H}_C &\leq m_1 + m_2 + m_4 - m_2^D
\end{align*}
\]  

(A.6a - A.6f)

Applying the effective flow rate ratios \( m_j \) defined in equations (2.21a) to (2.21d), these constraints simplify to:

\[
\begin{align*}
    m_3 - m_2^D + 2m_1^D + m_2^D &\leq \tilde{H}_A \\
    \tilde{H}_A &\leq m_4 \\
    m_3 - m_2 + m_4 - m_1^D + m_2^D &\leq \tilde{H}_B \\
    \tilde{H}_B &\leq m_2 \\
    m_3 &\leq \tilde{H}_C \\
    \tilde{H}_C &\leq m_1
\end{align*}
\]  

(A.7a - A.7f)

and thus the critical line as given in equation (2.23) is obtained by combining equations (A.7a) and (A.7c).

### A.2 Nomenclature

The same notation as in defined in chapter 2 applies.
List of Abbreviations

3C-ISMB  Three-Column Intermittent Simulated Moving Bed
3F-SMB   Three-Fraction Simulated Moving Bed
3S-ISMB  Three-Fraction Intermittent Simulated Moving Bed (withdrawal of the strongest retained component during substep 2)
3W-ISMB  Three-Fraction Intermittent Simulated Moving Bed (withdrawal of the weakest retained component during substep 2)
API      Active Pharmaceutical Ingredient
EDM      Equilibrium Dispersive Model
ETH      Eidgenössische Technische Hochschule (Swiss Federal Institute of Technology)
FDM      Finite Difference Model
FVM      Finite Volume Model
HPLC     High Pressure Liquid Chromatography
I-SMB    Intermittent Simulated Moving Bed
JO       Japan Organo Corporation
PNT      Phenetole
SPL      Separation Processes Laboratory
TBP      4-tert-Butylphenol
TMB      True Moving Bed
## List of Figures

1.1 Scheme of a standard SMB unit in 2-2-2-2 configuration, i.e. each section consists of two columns. The dashed lines indicate the position of the inlet (feed and desorbent) and outlet (extract and raffinate) streams after one port switch. .................................................. 3

1.2 Scheme of an equivalent TMB process at steady state. ................................. 4

1.3 Three-zone SMB with raffinate rear-portion recycle. ................................... 6

2.1 Process scheme of closed loop intermittent simulated moving bed (I-SMB) chromatography. Feed (F) supply and withdrawal of raffinate (A) and extract (B) is conducted in substep I, whereas in substep II all inlet and outlet ports are closed. The black and grey arrows indicate the direction of the fluid and the solid flow, respectively. .................................................. 13

2.2 Process scheme of 3S-ISMB which follows directly from I-SMB and is characterized by an additional product stream, namely withdrawal of the most retained component (C) in substep II. .................................................. 14
2.3 Physical plane for 3S-ISMB where coordinates are the time and the space coordinate along the unit’s columns. Each species propagates along straight characteristics, whose slope is given by the reciprocal of the velocity in 2.1. The blue characteristics represent species A, the red characteristics species B and the green ones species C. The dotted line divides the time axis in substep I and II. .................................................. 14

2.4 Triangular region of complete separation for 3S-ISMB in the \((\hat{m}_2, \hat{m}_3)\) plane and critical line \((\hat{m}_3 \leq -\hat{m}_2 + \hat{H}_C - \hat{H}_B + \varphi \hat{H}_A)\) below which complete ternary separation is feasible. The critical line is shown for three different values of \(\hat{H}_C\) and subfigure (c) shows that the process becomes infeasible if \(\hat{H}_C \leq (2 - \varphi)\hat{H}_A + \hat{H}_B\). .................................................. 17

2.5 Process scheme of 3W-ISMB which is characterized by withdrawal of the least retained component (A) in substep II. ................................. 19

2.6 Physical plane for 3W-ISMB where coordinates are the time and the space coordinate along the unit’s columns. Each species propagates along straight characteristics, whose slope is given by the reciprocal of the velocity in 2.1. The blue characteristics represent species A, the red characteristics species B and the green ones species C. The dotted line divides the time axis in substep I and II. ................................. 19

2.7 Triangular region of complete separation for 3W-ISMB in the \((\hat{m}_2, \hat{m}_3)\) plane together with the critical line. In the case of 3W-ISMB the critical line has a positive slope which renders the process feasible for any combination of \(\hat{H}_i\)-values. The critical line is independent of \(\hat{H}_C\), therefore it does not intersect the triangular region below a certain selectivity between component B and C (see subfigure (b)), i.e. in these cases the region of complete separation is determined by \(\hat{H}_B\) and \(\hat{H}_C\) only. ......................... 21
2.8 Flowsheet of the experimental set-up consisting of two binary gradient pumps, four chromatographic columns equipped with an inlet and an outlet manifold and nine multiposition valves. .................................. 25

2.9 Experimental model system consisting of racemic $\gamma$-Phenyl-$\gamma$-butyrolactone (denoted by A and B) and the (-)-Tröger’s Base enantiomer (C) in pure Ethanol separated on Chiralpak AD$^+\text{Q}$ ($Q = 0.5$ ml/min, $c_{F,i} = 0.5$ g/l); P denotes the injection peak. .......................................................... 26

2.10 Graphical analysis of the model system according to 2.1. Triangle and critical line for complete separation are shown for both the 3W-ISMB process (a) and the 3S-ISMB process (b). In both cases the upper limit of $\phi = 1$ was chosen and the extra-column dead volume was neglected. Moreover, (b) shows that 3S-ISMB is infeasible for this model system. ................................. 28

2.11 (a) Operating point of the four experimental runs $\alpha$ to $\delta$ represented in the $(\bar{m}_2, \bar{m}_3)$ plane. Two critical lines are shown; the one in red applies for run $\alpha$ only, whereas the black one applies for runs $\beta$ to $\delta$. The upward shift is due to a smaller value of $\bar{m}_4$. (b) Purity of the three product streams plotted against the $\bar{m}_2$-value of the operating point. ........................................... 28

3.1 Process scheme of closed loop intermittent simulated moving bed (I-SMB) chromatography. Feed and desorbent supply as well as withdrawal of the product streams raffinate and extract is conducted during in substep 1, whereas in substep 2 all inlet and outlet ports are closed. After the end of substep 2 the ports are switched in direction of the fluid flow and substep 1 is repeated. ................................................................. 40
3.2 Process scheme of the three column intermittent simulated moving bed (3C-ISMB) process. In the first substep the unit is operated fully identical to I-SMB as described in figure 3.1 and also the second substep is analogous to I-SMB in the sense that neither inlet nor outlet streams are provided to the unit. The fundamental difference of 3C-ISMB to conventional I-SMB resides in the fact that no fourth column is used to regenerate the solvent. A stream containing the weakly retained component is directly recycled from section III to section I which is feasible because section I is almost completely regenerated at the end of substep 1. Thus it can be used for adsorbing the weakly retained component, i.e. the task devoted to section IV in conventional I-SMB.

3.3 Simulated internal concentration profiles: (a) I-SMB at the beginning of the switching time, (b) I-SMB at the end of substep 1, (c) I-SMB at the end of substep 2, (d) 3C-ISMB at the beginning of the switching time, (e) 3C-ISMB at the end of substep 1, (f) 3C-ISMB at the end of substep 2. The greyed part illustrates either the section featuring stagnant flow (I-ISMB) or the non-existing section (3C-ISMB). The profiles were calculated using the system parameters given in table 3.1 and the operating parameter given in table 3.2 (Sim F).
3.4 Simulation based analysis of the purity levels achieved for conventional I-SMB for a fixed operating point in the \((m_{I}, m_{IV})\)-plane (filled black box) and total feed concentrations of (a) 1 g/l, (b) 5 g/l, (c) 10 g/l, and (d) 15 g/l. The solid lines indicate the boundaries of complete separation and regeneration according to Triangle Theory whereas all operating points yielding purities of at least 99.9% for both product streams are indicated with a green (●)-symbol and the letters ”E+R”. Correspondingly, all operating yielding only an extract (raffinate) purity of at least 99.9% are marked with a red (blue) (●)-symbol and the letter ”E” (“R”). For the sake of completeness, all other operating points studied are indicated with a grey (●)-symbol.

3.5 Simulation based analysis of the purity levels achieved for 3C-ISMB for a fixed operating point in the \((m_{I}, m_{IV})\)-plane and total feed concentrations of (a) 1 g/l, (b) 5 g/l, (c) 10 g/l, and (d) 15 g/l. The notation is given in the caption of figure 3.4.

3.6 Simulation based analysis of the purity levels achieved for conventional I-SMB for a fixed operating point in the \((m_{II}, m_{III})\)-plane and total feed concentrations of (a) 1 g/l, (b) 5 g/l, (c) 10 g/l, and (d) 15 g/l. The notation is given in the caption of figure 3.4, additionally an unfilled black box indicates the operating points used for deriving figure 3.4.

3.7 Simulation based analysis of the purity levels achieved for 3C-ISMB for a fixed operating point in the \((m_{II}, m_{III})\)-plane and total feed concentrations of (a) 1 g/l, (b) 5 g/l, (c) 10 g/l, and (d) 15 g/l. The notation is given in the caption of figure 3.6.
3.8 Influence of the $m_{IV}$ safety margin on the real region of complete separation for 3C-ISMB. The safety margin steadily increases from figure (a) to (d) and the $m_{IV}$-value is indicated in each figure. The same notation as in figure 3.4 applies.

3.9 Simulation based analysis of the purity levels achieved for I-SMB (a and c) and 3C-ISMB (b and d) under highly non-linear chromatographic conditions, i.e. at a total feed concentration of 200 g/l. The same notation as in figure 3.4 applies.

3.10 Comparison of (a) productivity and (b) solvent consumption for the optimal operating points tabulated in table 3.3.

4.1 Flowsheet of the experimental 3C-ISMB set-up consisting of four pumps, three chromatographic columns, each equipped with an inlet and an outlet manifold which are connected to six multi-position valves. The small bottle labeled with BT is a small buffer tank with a volume of approximately 1 ml that is used between the recycle outlet and the sucking side of the recycle pump in order to facilitate the removal of trapped air bubbles in the recycle line. It is noted that the conventional I-SMB set-up is easily realized by simply adding a fourth column and consequently adapting the switching procedure.

4.2 Pressure versus cycle number during run B: The dashed lines indicate a changes of the operating mode, namely the unit was operated from cycle 1 to 12 in optimized I-SMB mode, from cycle 13 to 20 in 3C-ISMB mode without changing flow rates and switch time and from cycle 21 to 28 in optimized 3C-ISMB, i.e. at the maximum allowable pressure drop.
4.3 Results of run A: (a) Purities of the product streams versus the cycle number and operating points in the \((m_{II}, m_{III})\)-plane. (b) Concentrations in the product streams raffinate (solid lines) and extract (dashed lines) versus the cycle number, the lines without marker represent the concentrations of the polluting species, i.e. component A (B) in the case of the raffinate (extract). In both figures, the dashed vertical lines indicate a change in the operating conditions, namely optimized I-SMB (shown as \(\bigcirc\) in the operating parameter plane) from the begin until cycle 12, non-optimized 3C-ISMB (\(\square\)) from cycle 13 to 20 and optimized 3C-ISMB (\(\diamond\)) from cycle 21 to 28.

4.4 Results of run B: (a) Purities of the product streams versus the cycle number and operating points in the \((m_{II}, m_{III})\)-plane. (b) Concentrations in the product streams raffinate (solid lines) and extract (dashed lines) versus the cycle number. The same notation as in figure 4.3 applies.

4.5 Results of run C: (a) Purities of the product streams versus the cycle number and operating points in the \((m_{II}, m_{III})\)-plane. (b) Concentrations in the product streams raffinate (solid lines) and extract (dashed lines) versus the cycle number. The same notation as in figure 4.3 applies.

4.6 Results of run D: (a) Purities of the product streams versus the cycle number and operating points in the \((m_{II}, m_{III})\)-plane. (b) Concentrations in the product streams raffinate (solid lines) and extract (dashed lines) versus the cycle number. The same notation as in figure 4.3 applies.

4.7 Results of run E: (a) Purities of the product streams versus the cycle number and operating points in the \((m_{II}, m_{III})\)-plane. (b) Concentrations in the product streams raffinate (solid lines) and extract (dashed lines) versus the cycle number. The same notation as in figure 4.3 applies.
4.8 Results of run F: (a) Purities of the product streams versus the cycle number and operating points in the \((n_{HI}, n_{HI})\)-plane. (b) Concentrations in the product streams raffinate (solid lines) and extract (dashed lines) versus the cycle number. In both figures, the dashed vertical lines indicate a change in the operating conditions, though the unit is always run in optimized 3C-ISMB mode, decreasing feed flow rates are studied, i.e. the operating point is stepwise moved from ○ (cycle 1 to 12) towards operating ◊ (cycle 21 to 28). Besides that, the same notation as in figure 4.3 applies.

4.9 Summary of all experimental runs: (a) Operating points in the operating parameter planes. (b) Productivity of runs A-E. The dashed vertical lines indicate a change in the operating conditions, i.e. they represent a change from optimized I-SMB (cycles 1-12) to non-optimized 3C-ISMB (cycles 13-20) and optimized 3C-ISMB (cycles 20-28). (c) Productivity vs. total feed concentrations for runs A-F and the three modes of operation. (Note: In Run E, cycle 26 the weighted mass of the collected product streams is erroneous due to a spill of product solution. Therefore the corresponding point is represented as filled diamond and not taken into account for drawing the connecting line.)

5.1 Overview on the general design methodology proposes in this work (s represents the stage number).

5.2 A 3C-ISMB cascade in a continuous setting. Buffer 2 is needed because switching time and step ratio of the two units are generally not equal.
5.3 Overall performance of a hypothetical 3C-ISMB cascade as a function of
the stage coupling policy and the relative selectivities: (a) illustration of
parameter δ, (b) overall performance versus parameter δ for extract stream
(case 1) and raffinate stream coupling (case 2). . . . . . . . . . . . . . . . . 107

5.4 (a) Soczewinski plot for Nadolol using the binary eluent mixture Hept-
ane Ethanol. The open symbols are measurements and lines are fitted
according to 5.13. (b) Chromatogram of a pulse injection using Hept-
ane/Ethanol/DEA 30/70/0.3 (v/v/v). . . . . . . . . . . . . . . . . . . . . 111

5.5 Frontal Analysis of the quaternary mixture at a total feed concentration
of (a) 5 g/l, (b) 10 g/l, (c) 15 g/l, and (d) 20 g/l. Open symbols repre-
sents the experimentally measured concentration profile by offline analysis
of the collected fractions whereas the solid line represents the simulated
concentrations profiles using the parameters of isotherm Q listed in table
5.2]. . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 113

5.6 Frontal Analysis of the ternary mixture at (a) a total feed concentration
of 8.7 g/l using Heptane/Ethanol/DEA 30/70/0.3 (v/v/v), and (b) a to-
tal feed concentration of 1.9 g/l using Heptane/Ethanol/DEA 40/60/0.3
(v/v/v). Open symbols represents the experimentally measured concentra-
tion profile by offline analysis of the collected fractions whereas the solid
line represents the simulated concentrations profiles using the parameters
of isotherm T and T_{dil}, respectively, listed in table [5.2]. . . . . . . . . . . 115

5.7 Region of complete separation in the \((m_2, m_3)\)-plane for the split ABP/C
calculated from the parameters of isotherm Q (see table [5.2]) for total feed
concentrations of 5 g/l, 10 g/l, and 15 g/l. The corresponding operating
points in \((m_1, m_4)\)-plane and \((m_2, m_3)\)-plane of experiments 1.1 to 1.4 are
represented by circles (5 g/l), squares (10 g/l), and diamonds (15 g/l). . . . 118
5.8 Region of complete separation in the \((m_2, m_3)\)-plane for the split AB/P calculated from the parameters of isotherm \(T\) ((a)-(c)) and isotherm \(T_{dil}\) ((d)) (see table 5.2) for total feed concentrations of: (a) 2.5 g/l, (b) 2.5 g/l, (c) 3.3 g/l, and (d) 1.9 g/l. The corresponding operating points in \((m_1, m_4)\)-plane and \((m_2, m_3)\)-plane of experiments 2.2 to 3 are represented by circles (operating point (a)), squares (operating point (b)), and diamonds (operating point (c)). Note that the eluent composition for the experiments represented in figure (d) differs from the other three subplots.

7.1 Influence of the number of cells used in the finite volume code on the accuracy of the results: (a) Fixed number of cells, varying concentrations; (b) Fixed concentration (25% of the maximum values), varying number of cells. The following parameters were used: \(H_1=1.41\), \(K_1=-0.033 \text{ l/g}\), \(H_2=2.15\), \(K_2=0.031 \text{ l/g}\), \(L_{col} = 25 \text{ cm}\), \(D_{col} = 0.46 \text{ cm}\), \(\epsilon = 0.61\), and 500 theoretical plates. It is further noted that the concentration ratio was kept constant and that concentrations are indicated in terms of percentage of their maximum values, being \(c_1 = 24.6 \text{ g/l}\) and \(c_2 = 90.90 \text{ g/l}\). Finally, the retention time is given in dimensionless form.

7.2 Frontal analysis on 4-\textit{tert}-Butylphenol: (a) Breakthrough experiments (orange lines) in comparison to numerical simulations (blue lines); (b) Adsorption isotherm where the circles represents the experimental measurements determined from figure (a) and the solid line the corresponding Langmuir isotherm with \(H_{\text{TBP}} = 2.15\) and \(K_{\text{TBP}} = 0.031 \text{ L/g}\). (25 cm Zorbax 300SB-C18 column, \(Q = 1.2 \text{ ml/min}, V_{\text{inj}} = 4 \text{ ml}\).
7.3  Frontal analysis on Phenetole: (a) Breakthrough experiments (orange lines) in comparison to numerical simulations (blue lines); (b) Adsorption isotherm where the circles (squares) were calculated from the shock velocity of the desorption step assuming an Anti-Langmuir isotherm (from a mass balance over the adsorption step) using the experimental profiles of figure (a). The solid line represents the Anti-Langmuir isotherm fitted to the values obtained by the shock velocity method resulting in $H_{\text{PNT}} = 1.41$ and $K_{\text{PNT}} = -0.033 \text{ L/g}$. (5 cm Zorbax 300SB-C18 column, $Q = 1.2 \text{ ml/min}$, $V_{\text{inj}} = 4 \text{ ml}$) 139

7.4  Illustration of the classical delta-shock experiment (orange line) where the column was first equilibrated for 5 min with pure mobile phase. It was then saturated for 35 min with a 24.0 g/L Phenetole solution which was displaced by a 90.0 g/L 4-tert-Butylphenol solution. After another 35 min the column was regenerated by feeding pure mobile phase. The blue (green) line represent an analogous sequence of inlet step changes, however the 4-tert-Butylphenol solution (Phenetole solution) was replaced by pure mobile phase. The figure nicely illustrates, that the material being present in the overlapping part of the blue and green curves, accumulate within a spike when the substances are interacting. (25 cm Zorbax 300SB-C18 column, $Q = 1.2 \text{ ml/min}$, $c_{\text{PNT}} = 24.0 \text{ g/L}$, $c_{\text{TBP}} = 90.0 \text{ g/L}$) 141
7.5 Influence of impurities on the determination of the Phenetole adsorption isotherm: (a) Analytical injections of the unpurified and distilled Phenetole solutions; (b) Frontal analysis using unpurified Phenetole (25 cm Zorbax 300SB-C18 column, $Q = 0.8$ ml/min, $V_{\text{inj}} = 5$ ml); (c) Frontal analysis using 1x distilled Phenetole (25 cm Zorbax 300SB-C18 column, $Q = 1.2$ ml/min, $V_{\text{inj}} = 4$ ml); (d) Delta-shock experiments using unpurified and 1x distilled Phenetole (5 cm Zorbax 300SB-C18 column, $Q = 0.7$ ml/min, $c_{\text{PNT}} = 20.0$ g/L, $c_{\text{TBP}} = 75.0$ g/L).

7.6 Phase separation across the travelling spike. Sample 13 was collected just before the spike, whereas the milky solution of sample 14 was collected right at the beginning of the relatively broad spike.

7.7 Effect of the flow rate on the development of a fully developed spike. (25 cm Zorbax 300SB-C18 column, $c_{\text{PNT}} = 24.0$ g/L, $c_{\text{TBP}} = 90.0$ g/L)

7.8 Effect of feed concentration (feed concentrations reported in table 7.1): (a) Experimental (orange) and numerically simulated (blue) elution profiles for the sequence 5 min MP - 25 min PNT - 10 min MP - 25 min TBP - 25 min MP using different feed concentrations. The inset plots demonstrate that the position of both shock fronts are well captured by the model. (b) Ditto, however without feeding MP between the PNT and TBP solutions. Here, the inset plot represents a zoom on the spike. (5 cm Zorbax 300SB-C18 column, $Q = 1.2$ ml/min)

7.9 Effect of interaction time: Experimental (orange) and numerically simulated (blue) elution profiles for the sequence 5 min MP - 25 min PNT - $t_{\text{int}}$ min MP ($t_{\text{int}} = 0, 1.5, 3.0, 7.0, 10.0$) - 25 min TBP - 25 min MP. The inset plot represents a zoom on the relevant shock fronts. (15 cm Zorbax 300SB-C18 column, $Q = 1.2$ ml/min, $c_{\text{PNT}} = 24.6$ g/L, $c_{\text{TBP}} = 90.9$ g/L).
7.10 Effect of interaction time: Experimental (orange) and numerically simulated (blue) elution profiles for the sequence 5 min MP - 25 min PNT - $t_{\text{int}}$ min MP ($t_{\text{int}}$ = 0, 1.5, 3.0, 7.0, 10.0) - 25 min TBP - 25 min MP. The inset plot represents a zoom on the relevant shock fronts. (25 cm Zorbax 300SB-C18 column, $Q$ = 1.2 ml/min, $c_{\text{PNT}}$ = 24.6 g/L, $c_{\text{TBP}}$ = 90.9 g/L).

7.11 Effect of column length: Selected experimental profiles of figures 7.8 to 7.10 for (a) the case with no interaction, i.e. $t_{\text{int}}$ = 10 min and (b) the case with immediate interaction, i.e. $t_{\text{int}}$ = 0 min. The solid black lines in the physical plane illustrate the shock velocities according to equilibrium theory.

7.12 Comparison of experimental and theoretical retention time of the spike: (a) Summary of all experiments where an experimental spike was observed, (b) Retention time of the spike versus column length for $t_{\text{int}}$ = 0 min. Note that the retention times were corrected for dead time and equilibration times for better comparison. Furthermore, the width of the experimental spike is indicated with a solid blue line.

7.13 Binary frontal analysis experiments using a concentration ratio PNT:TBP of 1:3 and increasing concentrations from (a) to (f) as indicated. The experiments were repeated at least twice and the repetitions are indicated as exp(2) and exp(3) for the first and the second repetition, respectively. Red symbols stands for the more retained component TBP, whereas blue symbols denote PNT. Moreover, the solid black lines denote the solution of the numerical simulation using the generalized Bi-Langmuir isotherm, whose parameters are given in table 7.2.

7.14 Binary frontal analysis experiments using a concentration ratio PNT:TBP of 1:1 and increasing concentrations from (a) to (c) as indicated. The same notation as in 7.13 applies.
7.15 Binary frontal analysis experiments using a concentration ratio PNT:TBP of 3:1 and increasing concentrations from (a) to (d) as indicated. The same notation as in 7.13 applies.

7.16 Binary displacement experiments where the column was initially saturated with: (a)-(c) a 12 g/l PNT solution that was displaced by a TBP solution having a concentration of 20 g/l (fig. (a)), 40 g/l (fig. (b)), and 80 g/l (fig. (c)). In (d)-(f) the same sequence was performed, however at an initial PNT concentration of 18 g/l. The same notation as in 7.13 applies.

7.17 Binary displacement experiments where the column was initially saturated with a 24 g/l PNT solution that was displaced by a TBP solution having a concentration of 20 g/l (fig. (a)), 40 g/l (fig. (b)), and 80 g/l (fig. (c)). The same notation as in 7.13 applies.

7.18 Peculiar adsorption behavior of Phenetole observed on a 5 cm Zorbax Extend-C18 column: Both the frontal analysis shown in figure (a) as well as the binary experiments shown in figure (b) suggest a type V isotherm.
List of Tables

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1</td>
<td>System characteristics</td>
<td>27</td>
</tr>
<tr>
<td>2.2</td>
<td>Operating conditions for the experimental runs $\alpha$ to $\delta$ with substep durations of 1.50 min and 3.98 min for substep I and substep II</td>
<td>30</td>
</tr>
<tr>
<td>2.3</td>
<td>Concentrations of all three solutes in the outlet streams and corresponding product purities for runs $\alpha$ to $\delta$</td>
<td>31</td>
</tr>
<tr>
<td>3.1</td>
<td>Characteristics of the binary system</td>
<td>42</td>
</tr>
<tr>
<td>3.2</td>
<td>Separation performance of the optimal operating points with respect to productivity for a fixed operating point in the $(m_I, m_{IV})$-plane, i.e. the vertices of the real triangles for I-SMB and 3C-ISMB as shown in figures 3.4 and 3.5 as well as 3.8f and 3.9. The differences of productivity and solvent consumption are given in terms of $(PR_{3C-ISMB}/PR_{I-SMB} − 1)$ and $(SC_{3C-ISMB}/SC_{I-SMB} − 1)$.</td>
<td>55</td>
</tr>
<tr>
<td>3.3</td>
<td>Separation performance of the optimal operating points maximizing productivity and minimizing solvent consumption. The differences of productivity and solvent consumption are given in terms of $(PR_{3C-ISMB}/PR_{I-SMB} − 1)$ and $(SC_{3C-ISMB}/SC_{I-SMB} − 1)$.</td>
<td>64</td>
</tr>
</tbody>
</table>
4.1 Characteristics of the binary model system ............................................. 73
4.2 Design equations for I-SMB for negligible dead volume and lab scale plant
where dead volume and pressure drop along the dead volume has to be
accounted for .................................................................................................. 74
4.3 Design equations for 3C-ISMB for negligible dead volume and lab scale
plant where dead volume and pressure drop along the dead volume has to
be accounted for .............................................................................................. 75
4.4 Operating conditions and separation performance of the experimental I-
SMB and 3C-ISMB runs; the position of the operating points in the oper-
ating parameter plane are shown in figure 4.9a, respectively in figures 4.3a
to 4.8a ........................................................................................................... 80
5.1 Parameters of the Soczewinski equation (see al's figure 5.4) .................... 111
5.2 Isotherm parameters used for the design of the 3C-ISMB experiments ........ 114
5.3 Overview of all 3C-ISMB experiments performed .................................... 116
5.4 Performance of the overall 3C-ISMB cascade applying the re-scaling ap-
proach (see section 5.3.2) ............................................................................. 122
7.1 Summary of all experiments carried on the stationary phase Zorbax 300SB-
C18 applying a volumetric feed flow rate of 1.2 ml/min and the sequence
\[ t_{eq} \rightarrow t_{PNT} \rightarrow t_{int} \rightarrow t_{TBP} \rightarrow t_{reg} \] with \( t_{eq} = 5 \) min, \( t_{PNT} = t_{TBP} = t_{reg} = 25 \)
min and \( t_{int} \) according to the values given in column 2. The elution time
of the experimental delta shocks is compared to the equilibrium theory
solution. In all cases the extra-column dead time of 0.99 min is included .... 153
7.2 Parameters of a generalized Bi-Langmuir isotherm fitted to binary break-
through and displacement experiments ....................................................... 155
Bibliography


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