Control and optimization of continuous chromatographic separation processes

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**CONTROL AND OPTIMIZATION OF CONTINUOUS
CHROMATOGRAPHIC SEPARATION PROCESSES**

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2012

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I would like to dedicate this thesis to my loving parents ...

Acknowledgements

We started this work from scratch, that is, we developed everything for ourselves including numerical solution methods, optimization routines, controller algorithm codes, and laboratory setup. These could not have been done without the help of numerous technical and knowledgeable people who supported us with benevolence.

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Abstract

The modern trend of pharmaceutical technology has been greatly shifted towards single or pure enantiomeric drugs due to strict regulations imposed by drug approval authorities in order to obtain higher drug efficiency and to alleviate undesirable side effects. Enantiopure compounds can be accessed either by organic synthesis or by resolution techniques. Recently, chromatographic separation has become the preferred method for its cost effectiveness, ease of operation, and flexibility as it employs variety of processing materials and methods supported by rich theoretical background.

Simulated moving bed (SMB) has been extensively used for the separation of chemicals in the past 50 years, though its application to enantioseparation is relatively new. Supported by the benefits of counter-current mode of operation, SMB has become the method of choice for large-scale operations. However, SMB is a complex process both in terms of design and operation. There have been numerous efforts to emulate SMB by simpler processes. Many of them are based on using a single column with a recycle stream.

In this work, we proposed an improved single-column chromatographic (ISCC) separation process. The term ‘improved’ refers to both conceptual and physical modifications. We proposed a novel fraction collection scheme and allowed overlapped peaks from adjacent cycles. We also modified the fraction collection mechanism in order to facilitate online monitoring.

Another advantage of the ISCC process is its large degree of freedom as injection volume, cycle time, desorbent flow rate, feed concentration and fraction-collection intervals can all be decision variables in this process.

Every continuous process needs some sort of feedback from the process for quality control and monitoring. The chromatographic separation processes are usually monitored via low-frequency devices such as analytical high-performance liquid chromatography (HPLC) systems. Alternatively, innovative approaches have been taken to improve the sampling rate using combination of various detectors, peak deconvolution, etc. The design of an efficient online monitoring system is still an open problem.

In this work, we proposed an online monitoring system, which comprises of two parallel HPLC units with customized peripherals in order to improve the accuracy and sampling rate. The proposed device can be readily coupled to the ISCC process. It is also less expensive compared to the similar commercial units.

Minimizing operation costs and maximizing productivity are necessary for a profitable operation. They are typically complex functions of process inputs, and the operation might be limited by certain constraints as well. Similarly, optimization is not straightforward for the ISCC process as there

are several variables contributing to a multi-dimensional solution space. On the other hand, process outputs have opposing effects on the profitability of the process. As a result, there may not be a single dominating solution as the best operating point.

We adopted a multi-objective optimization technique based on genetic algorithm (GA) to achieve maximum productivity and minimum desorbent requirement in the region constrained by product specifications and hardware limitations for the separation of guaifenesin enantiomers. The optimization results along with the contribution of decision variables were discussed using Pareto fronts, which identify non-dominated solutions. Optimization results of a similar simulated moving bed process were also included to facilitate comparison with a continuous chromatographic separation process.

We developed efficient numerical techniques for simulating chromatographic model equations as a prerequisite for process optimization. Existing solution techniques, i.e. finite-difference and finite-element methods, were briefly reviewed and compared with finite-volume method, which so far has been little applied to the solution techniques of model equations in the chromatographic community. We identified van Leer flux limiter in the realm of total variation diminishing (TVD) schemes and third-order weighted essentially non-oscillatory (WENO) scheme as competitive and remarkable candidates in terms of speed and accuracy.

Continuous operation requires automatic control to handle disturbances and implement setpoint tracking. Model predictive control (MPC) has been the method of choice for controlling multi-input multi-output chemical processes with constraints. MPC has the advantage of efficient setpoint tracking and disturbance rejection via predicting the process evolution. Moreover, MPC can find optimal trajectories in the dynamic solution space, for example, when the process has yet to reach steady state or when it is under the effect of any disturbance.

We implemented a ‘cycle to cycle’ MPC scheme with the objectives of optimizing the operation profitability while fulfilling the product constraints (i.e., purity and recovery) and hardware limitations (e.g., maximum allowable pump flow rate). Injection volume, desorbent flow rate, and three cut intervals were considered as manipulated variables, while change in feed concentration and isotherm parameters were taken as unmeasured disturbances. The controller was successfully tested on a virtual plant for the separation of guaifenesin enantiomers for setpoint change in purity/recovery values and also for disturbance rejection.

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Chapter 1

Introduction

Application of chirally active drugs is not new; in fact, it goes back to the year 1677 when quinine was discovered as an effective treatment of malaria [1]. However, the tremendous effects of individual enantiomers both in positive and negative ways have been acknowledged just in the past 30 years. The changes they have brought in are technically and economically ground breaking. In early 1990s, 30% of drugs was racemate or diastromer. In 2003, there was not even a single racemic drug brought to the US market and in 2004, the only drug introduced as a racemate was Gemifloxacin [2].

Literature reports vast amount of research and applications related to single-enantiomer drugs [3, 4]. In fact, current activities are not limited to developing newly discovered chiral compounds; chiral switches are also an attractive field of research and marketing [2]. Chiral switches are drugs that have already been claimed, approved and/or marketed as racemates or as mixtures of diastereomers, but have since been reconsidered as single enantiomers [3].

Even before approval and commercialization, accessing enantiopure compounds in relatively large amount is necessary for lifting the time to market barrier, which is typically a long procedure for pharmaceuticals. Chromatographic separation processes have already established themselves as key processing methods in this regard. Therefore, developing time and cost-effective chromatographic separation processes is essential as a supporting step of drug discovery, development, and commercialization.

Chromatographic separation process design schemes vary from single-column batch separation (also known as elution mode [5]) to fully automated simulated moving bed (SMB), which resembles a continuous true moving bed (TMB) process [4]. The objectives of developing new processes are primarily speed of separation and reducing the total production cost. Observing the ever-growing stringent regulations, quality control, and safety may also be other motivations.

There is no cure-all for all problems and a compromise might be necessary for any specific demand. For instance, batch operation is well suited for varying feeds and small-scale research activities, while at large scale for a fixed production, an SMB process is favorable and usually outperforms the batch operation.

Although SMB is one of the most advanced chromatographic separation methods, which boosts productivity and reduces the operation costs, it is relatively hard to design and control due to its hybrid nature [6]. It also demands significant capital investment. As a result, there have been some efforts to find simpler processes, which

can resemble SMB in characteristics [7, 8, 9, 10].

In order to investigate the performance of different processes on a fair basis, they must be examined at their optimal operating points. In addition, parameters must be defined in a consistent manner, including decision variables, process scale, constraints, and objective functions. There might be a trade-off necessary among objective functions as they may not be simultaneously maximized or minimized at a single operating point.

The need for an effective modeling method for in-depth studies of the process has emerged since the inception of research in this field. Various modeling schemes have been proposed with different degrees of complexity. As a general trend, attention has first been focused on simplified modeling methods for which analytical solutions existed [11, 12]. Later, mass transfer and axial dispersion effects were added for more realistic process descriptions [5]. With the increasing degree of complexity in chromatographic process modeling, accuracy and computational time become important especially for large-scale process optimization and online optimizing control problems [6, 13, 14].

Using an efficient monitoring system is imperative for the operation of any chromatographic process in a continuous manner. The target is the fast and accurate measurement of product concentration. Besides, it must be robust with respect to variations in process operating condition (pressure, concentration, etc.) [6]. Most often there is a need for specific modifications in the process structure to embed a certain monitoring system. In the light of these objectives, there have been several attempts to resolve the challenging obstacles, though the design of an efficient online monitoring system is still an open problem [15, 16].

Offline optimization does not guarantee finding the best optimal trajectory in the dynamic solution space and in the presence of disturbances, it may not find the corresponding optimal solutions. Model predictive control (MPC) has been widely used in research and industry in the past 30 years [17, 18, 19]. An MPC scheme in fact hinges on solving an online optimization problem. Therefore, it has a lot to share with conventional offline single-objective optimization techniques, though it can also handle setpoint tracking and disturbance rejection tasks.

MPC is popular in the chemical processes including applications of chromatographic separation in particular for (semi-)continuous processes such as simulated moving bed (SMB) [6, 18, 20, 21]. Although there are a few number of applications of MPC in batch chromatographic separation processes [22, 23], their intrinsic nonlinearity, stringent product specifications, and large number of input-output variables necessitate application of an online optimizing control algorithm and make it a challenging problem.

1.1 Contributions of this work

In this work, we developed and realized an improved single-column chromatographic (ISCC) separation process to eliminate the inefficiencies of usual stacked injection chromatography [24] that is, low productivity and high desorbent requirement while utilizing its inexpensive and simple design. The term ‘improved’ refers to both physical and conceptual improvements in the process; the feed injection and fraction collection mechanisms of commercial HPLC units were redesigned to facilitate the mode of

operation and online monitoring. The process performance is also improved through allowing overlapped peaks from adjacent cycles. The fraction collection mechanism divides the elution profile into four fractions. This fraction collection scheme is advantageous in the sense that it offers a better degree of freedom in search for optimal operating conditions especially when peaks are overlapped.

As mentioned earlier, developing an efficient online monitoring system especially for chiral separation is still an open challenge. We developed a novel online monitoring system, which operates on a cyclic basis. This is intended to return average purity/recovery measurements for product quality control and closed-loop automatic operation. Two HPLC units each comprising of an analytical column, a UV detector, and an injection valve are the main components of the proposed online monitoring system. This arrangement improves the sampling rate and increases the accuracy of analysis. In addition, two customized intermediate vials are designed and realized to connect the online monitoring system to the fraction collection mechanism as described in Chapter 2. The role of the intermediate vials is to obtain the average concentration of products per every cycle of operation/analysis. Therefore, they are made in such a way that perfect mixing is achieved and cross-contamination between collection cycles is minimized. We have filed a patent for the process design and its online monitoring system.

For numerical solution techniques, there must be a compromise between speed and accuracy in general, while stability must be guaranteed at all costs. We investigated several numerical methods in search for the best solution technique for chromatographic model equations. We realized that finite-volume method is in general superior to finite-difference and finite-element methods. As discussed in Chapter 3, under the broad family of finite-volume schemes, total variation diminishing (TVD) [25] and weighted essentially non-oscillatory (WENO) [26] schemes were found the best candidates. Among them, van Leer flux limiter and third order WENO scheme were almost equal, though for the ease of implementation, we widely used the WENO scheme for discretization of partial differential equations arising in this work.

In Chapter 4, we compare single-column chromatography and simulated moving bed at optimal operating point via analytical solutions available for linear and Langmuir isotherms. This method offers a shortcut way for identifying the optimal solutions, and helps to understand the theoretical degrees of freedom for these processes.

We must emphasize that experimental and theoretical optimization studies are different and they have their merits and demerits. With powerful computers, and in particular with parallel computing facilities available, theoretical optimization can be quick and cost effective provided that method-development and parameter-estimation tasks have already been carried out. In Chapter 5, the ISCC process is optimized offline over a wide range of operating parameters namely, injection volume, cycle time, desorbent flow rate, feed concentration, and three cut intervals with the objectives of maximizing productivity and minimizing the desorbent requirement for different product purity and recovery specifications. The resulting solutions were obtained through genetic algorithm and presented as a set of Pareto-optimal points providing a way for quantification of the best achievable sets of productivity and desorbent requirement values. We also showed that there are certain key relations between various decision variables on the Pareto fronts.

Based on the offline optimization results, in Chapter 6, we propose an online optimizing control scheme, which draws on ‘cycle to cycle’ mode of operation [6]. In this way,

the feedback data is provided to the controller on a cyclic basis. In fact, this mode perfectly suits the online monitoring system we designed and realized for the ISCC process.

We propose a model predictive control (MPC), which utilizes an empirical model for prediction. Five inputs as injection volume, desorbent flow rate, and three cut intervals, and five outputs as purities, recoveries, and a performance function which carries the effects of productivity and desorbent requirement are considered for the empirical model. The empirical model is identified via system identification techniques. Despite its relatively simple structure, the MPC scheme can accomplish setpoint tracking and disturbance rejection tasks on a virtual plant with satisfaction.

The process setup was realized at the laboratory scale along with its dedicated online monitoring system and human-machine interface (HMI), which is in charge of interfacing with user, automatic operation, and data collection. The HMI is equipped with both manual and automatic modes of operation, which enables us to run the process safely and with minimal human intervention.

The list of publications from this thesis is given in Appendix F.

Chapter 2

Design of the ISCC Process and Its Online Monitoring System

Despite having a simple structure, the conventional stacked injections suffer from low productivity and high desorbent requirement, which mean low profitability. Simulated moving bed (SMB) however, was proposed as a pseudo-counter current, continuous process to address such issues. It can effectively boost profitability of chromatographic separations, but at the cost of higher complexity and capital investment.

In this chapter, we elaborate on the design and realization of improved single-column chromatographic (ISCC) separation process. This process offers better productivity compared to stacked injections, while it requires less capital investment compared to SMB.

Conventional feed injection and fraction collection systems were replaced with customized components facilitating simultaneous separation and online monitoring. They also give a better degree of freedom on decision variables, which serves for optimization studies.

In this process, four fractions are collected. Two fractions are highly pure in each product. The other two fractions have the role of controlling the purity of products, though they can be recycled for further separation similar to the recycling processes [27]. Prior to sampling and storage, the two product fractions are mixed in two separate intermediate vials for online monitoring.

Designing an online monitoring system is still an open problem for chromatographic separation of enantiomers. They still suffer from issues such as adverse effects of disturbances, frequent loss of calibration, low sampling rate, etc. Our proposed approach responds to several aspects including low sampling rate of online HPLC units, cross-contamination, cost of equipment, integration to process, etc. In the proposed approach, the intermediate vials have a crucial role. We propose a manifold of solutions for the design and realization of the vials, which will be discussed in Section 2.1.2. They include but not limited to an improved method of gas-liquid and liquid-liquid mixing, using an external shaker, using a baffle, and reducing dead volumes of the vials.

The process was realized in laboratory scale with a semi-preparative chiral stationary phase (CSP) column as the heart of the separation process. The operating parameters are implemented through a dedicated human-machine interface (HMI) software package developed for this process on site. It is also in charge of automatic injection

and fraction collection. The integrity of the process, the online monitoring system, and the HMI was validated in practice for steady state runs.

2.1 Process design

Chromatographic separation process design schemes vary from single-column batch separation (also known as elution mode [5]) to fully automated simulated moving bed (SMB) [28, 29]. Recently, other counter-current processes like multi-column solvent gradient purification (MCSGP) [30] have also been proposed. The main objective of introducing new processes is better profitability, though observing ever-growing stringent regulations, quality control, and safety may also be other motivations.

SMB has been in operation for more than half a century for multi-ton production of petrochemicals. More recently, it has been widely used for separation of fine chemicals, especially pharmaceuticals [4]. However, batch operation is still attractive for varying feeds and small-scale research activities. This can be attributed to the complexity of the SMB process, and the fact that it demands significant capital investment [31].

In the gap between small-scale and large-scale operations, there are chances for innovative designs, which can be hybrids of both batch and continuous operations. One example is the single-column process with a recycle stream. In this process, a portion of fractioned product which does not fulfill the purity requirements, is recycled and mixed again with the feed stream. It has been shown that with a proper design of feed injection schedule, after several cycles, a steady state condition can be achieved. Because of its unique feature, this process is called steady state recycling (SSR) [7, 32, 33].

This process is similar to the elution mode in that the injection and fractionation procedures are analogous. However, from dynamical point of view, its behavior is similar to the SMB process; although there are temporal variations within each cycle, a same pattern is followed from cycle to cycle after steady state has reached.

This process has proved its superior performance with respect to the elution mode. However, its productivity is typically lower and its solvent consumption is higher than a similar SMB process at large scale [27, 34]. Moreover, the design criteria are not straightforward if not harder than SMB [31].

Abunasser et al. [35] used a single-column setup in conjunction with an array of tanks to imitate SMB. Later, they extended the work to a two-column analogue setup [36]. They showed that with these methods, at equal productivity and product purity, the desorbent to feed ratio is much less compared to a single column without recycle. However, they showed that their setups can only imitate an equivalent SMB if a sizable number of tanks is used. They concluded that with proper design, it is possible to reduce the time and solvent needed to reach the cyclic steady state of SMB.

In another investigation, it was shown that periodic state of SMB can be reproduced by a single column with a plug-flow recycle stream [9, 37]. They showed that with a proper design, an identical value of product purity can be obtained at constant productivity, but it needs a rather sophisticated plug-flow recycle path comprising of a variable length tube and a moving piston. Their proposed method is generally less expensive and simpler than an equivalent SMB.

In general, since these systems have only one column, the problems arising from

packing differences in the array of columns in SMB are alleviated. Furthermore, the total pressure drop is lower in these design schemes and hence more efficient particles with smaller diameter can be used.

In this work, we have introduced an improved single-column chromatographic (ISCC) separation process where feed injection and fraction collection mechanisms of commercial HPLC units are redesigned to facilitate the mode of operation and online monitoring. In addition, operation flexibility is improved through variable injection volume, variable cycle time, an improved fraction-collection scheme, and allowing overlapped peaks from adjacent cycles as explained in Section 2.1.1. We have not considered recycling at this stage of process development though it can be an extension to this work.

2.1.1 Process description

In this section, we describe a binary separation by means of the ISCC process. The less retained compound and more retained compound are referred to as B and A, respectively. The tag numbers refer to the process flow diagram shown in Fig. 2.1. Feed, as a train of pulses, is injected by the arrangement of an HPLC pump (P1) and an 8 port, 2 position switching valve (V1). This method does not require any autosampler and reduces the sample injection time. In addition, this arrangement allows variable injection volumes through partial loop filling, which means injection volume can change in a gradual manner. This feature helps to search for the optimal point in the entire range of injection volume. The feed pump (P1) delivers the feed at a specified concentration and flow rate for a certain period of time. In this manner, an accurate mass throughput of solute is injected. Desorbent is delivered through a second HPLC pump (P2). The maximum desorbent flow rate is dictated by the maximum allowable pressure that the stationary phase Chiralcel OD can withstand (approximately 40-50 bar).

A semi-preparative column (C1) is used for separation. A typical chromatogram is shown in Fig. 2.2(a) for steady state operation (see Chapter 6 for a discussion on non-steady state operation). The eluted compounds are divided into four fractions as shown in Fig. 2.2(b). The start of collection is detected by the UV detector (D1) as the rising shoulder of the first peak elutes, and hence it is considered as the start of the first cycle. The consecutive start points are calculated with respect to this point. Although the elution profile might be continued to the next cycle as there is no limitation for baseline separation in this separation scheme.

The fraction collector is a 5 port, 4 position valve (V6), which resolves the elution profile into four fractions: the first fraction is rich in B. It is collected immediately after the first peak is detected. The second fraction is a mixture of A and B and is considered as a waste in this process scheme although it can be recycled to the feed for further purification. The third fraction which is rich in A, is collected in a similar fashion. Finally, the fourth fraction is collected as the second waste. It is worthy of attention that for a Langmuir-type isotherm, the fourth fraction is usually diluted and its total concentration is by far less than the second fraction. This fact is actually the primary reason for collecting two waste fractions separately. Nevertheless, the fourth fraction still has an important effect on the product purity. In summary, this fraction collection scheme offers three cut intervals as three degrees of freedom to the designer.

The contents of product fractions are sent to two intermediate vials (VI1/VI2) where

Figure 2.1: Schematic process flow diagram along with the online monitoring system.

they are well homogenized to obtain an average concentration values representing the entire respective fractions. Arrangements are provided for the injection of a small fraction from each vial to two parallel analytical columns (C2/C3) of the online monitoring system as shown in Fig. 2.1. The effluents from these columns are directed to two UV detectors (D2/D3) for concentration measurement. See Section 2.2 for further details on the online monitoring system. The contents of vials enriched in single enantiomers are collected in two separate product bottles at the end of every analysis/cycle.

2.1.2 Design of the intermediate vials

As mentioned earlier, product streams must be well mixed in the intermediate vials for every cycle of operation prior to analysis, but achieving perfect mixing is a tedious task. In this regard, minimizing vial dead volumes is necessary. Moreover, for typical mobile phases used in HPLC analysis, natural circulation is not sufficient to provide perfect mixing in such small vessels.

The schematic drawing of one of the vials is given in Fig. 2.3. The main part of the intermediate vial is a Swagelok sampling cylinder (www.swagelok.com). It was the best type of vessel we found for this purpose in the Singapore region. We had to make modifications in order to achieve desirable results. For instance, a proprietary insert was designed to minimize the dead volume of the outlet port as shown in Fig. 2.3. As the purging gas (helium) enters from the lower nozzle, the upward flow of gas also blocks the flow of liquid downward and hence isolates dead volumes under the outlet nozzle. This is a major difference compared to the normal way of purging liquid-filled vessels.

In summary, mixing was enhanced in several ways as follows:

(a)

(b)

Figure 2.2: Typical elution profiles: (a) train of consecutive eluted peaks; (b) allocation of cut intervals and fractions. t_{sc} is the start of cycle and dt_{c1} to dt_{c4} are the assigned cut intervals comprising one cycle time.

- The vial and its accompanying switching valve is mounted on a variable-speed external shaker, which provides orbital movement.
- The purging gas enters the vial from lower port and bubbles through the liquid holdup thus enhances mixing. Although the primary purpose is to pressurize the vial and regulate the purging speed.
- A small piece of tubing is used to create a deep-jet nozzle. The length of tubing is selected in a way that the inlet liquid is injected far beneath the liquid level, causing additional mixing.
- The tubing used as the deep-jet nozzle is slightly tilted. Therefore, it acts as a baffle and boosts the mixing.

Figure 2.3: Cross-section of the customized intermediate vial.

2.2 Design of the online monitoring system

Using an efficient monitoring system is imperative for operation of any chromatographic system in a continuous manner. The target is fast and accurate measurement of product concentration. In addition, it must be robust with respect to variations in process operating conditions (pressure, concentration, etc.) [6]. Optical detection is the method of choice for almost all solutions somehow, but they are certainly different

in terms of sampling frequency, and the way the monitoring system is connected to the process. In the following lines, we briefly cover the most popular monitoring systems available in the literature with special focus on the detection of chiral compounds.

The conventional approach specific to enantiomers is the combination of a UV detector and a polarimeter. Since enantiomers rotate the light in two different angles, the produced signal in a polarimeter is proportional to the difference between the concentrations of two enantiomers. On the other hand, a UV detector can give a cumulative measure of the concentrations of two enantiomers similar to achiral compounds. By careful calibration, it is possible to obtain both concentrations even in overlapped conditions in an online fashion. This method has been widely used in chiral separation technology including SMB processes. However, many researchers have emphasized that polarimeters need frequent calibration, and they are sensitive to pressure fluctuations and impurities in the fluid stream [6, 38, 39].

A similar approach is based on the application of circular dichroism (CD) along with a UV detector for separation/detection of enantiomers. This method has received some attention in the scientific literature [40], but it has not found its way to industrial applications very well [41].

For any specific substance, there is an optimum detection wavelength in spectrophotometry. Based on this fact, the possibility exists that several overlapping concentration profiles can be discriminated by using an efficient multi-wavelength detector, such as commercial diode array detectors. This has been a subject of several attempts in finding new online monitoring systems [37, 42], but its viability is still under question. In specific, since enantiomers have equal absorbance at different wavelengths, this method may not work for them.

Another approach is based on mathematical formulation; one can curve-fit an overlapped chromatograph with a suitable class of curves, for instance exponentially modified Gaussian (EMG) and deconvolve two or more peaks. This method has been discussed by several researchers [43, 44, 45]. Somehow, the accuracy of the curve-fittings in general is questionable, and may depend on the noise level and other influential factors in process and monitoring system.

Araujo et al. [45] presented an innovative online monitoring system for an SMB process by utilizing two UV detectors sharing the same light source. One of these detectors is located inside the SMB loop giving the total concentration similar to the conventional methods. The second detector is in fact a part of a custom-made analytical HPLC coupled to the SMB process by means of a unique valve arrangement. This configuration allows instantaneous sampling from a stream between two columns without disrupting the continuous flow. Thus, this system can measure the individual concentrations precisely but for a short moment.

It was shown by these researchers that this method offers a good sampling rate (approximately one sample per minute) and reasonable level of accuracy when the purity is compared with the simulated results. However, there have been some discrepancies with unclear sources between the data obtained from the UV detector which gives the total signal, and the data derived from the online HPLC.

Langel et al. [16] suggested a different monitoring system with the aim of emulating the conventional UV-polarimeter detectors. This online monitoring system which is a modified HPLC device, works on a cyclic basis. The cycles are synchronized with the cyclic operation of SMB process in their case and besides, no interruption is

imposed on the process. It comprises of four custom-made glass tanks, as intermediate collection vessels, an array of automatic valves, and an analytical HPLC system. The analytical HPLC comprises of standard components including an injection arm, a chromatographic column, and a UV detector.

The extract and raffinate streams are alternately collected in a pair of glass tanks and the other pair is washed with pure solvent to prevent cross-contamination between cycles. Once the products from one cycle are collected, the injection arm takes out a small sample from each tank and injects it into the analytical column. The resolved peaks are converted to concentration information through the calibration of the UV detector.

Despite its innovation factor, there are certain drawbacks with this system; first, the injection arm is a slow mechanism and it adds up unnecessary delay to the analysis time. Also, some difficulties may arise in working with this injection mechanism when the tanks need to be airtight. Second, this system consumes a considerable amount of solvent and the solvent is added to the products, which increases the cost of downstream processing as well. In addition, the time gap between two injections might become the bottleneck of this system, while addition of a second analytical HPLC could resolve this problem. Finally, no mixing is provided for the glass tanks in this system. Therefore, it is unclear whether the injected sample is a good representative of the average concentration in each cycle.

With regard to the above mentioned arguments, we introduce a novel online monitoring system here for quality control of products and closed-loop operation. It comprises of two customized HPLC systems, which can operate in parallel. There is no injection arm in this system. As a result, the time required for analysis is lower and moreover, the entire system is less expensive than similar commercial devices. It can also be coupled to the process without interruption. The device is described in details in the following sections.

2.2.1 System description

Based on the survey given above, our proposed online monitoring system has some parts to share with previous implementations, but it has novel features as well, which we will elaborate on them in the following paragraphs. The principle of measurement of the proposed system is analogous to an ordinary analytical HPLC: a pulse of product is injected into a stream of a desorbent (solvent) and is resolved in an analytical column. After the pulse elutes from the column, the peaks are analyzed in a UV detector. The concentrations are measured via light absorbance with the help of a calibration curve.

On the other hand, the need for embedding this monitoring system into the ISCC process necessitates major modifications in its sampling mechanism. As a matter of fact, our proposed approach is similar to what was suggested by Cavazzini et al. [15], Langel et al. [16], Araujo et al. [45], but it has its novelty especially in the way the products are collected and directed to the online monitoring system. Moreover, compared to conventional low-frequency, online HPLC systems, this system is a moderate-frequency detector. The main features of this system are summarized as follows:

- It is designed for binary separation of variety of materials in particular chi-

ral compounds. Although it can be used for multi-component separation with proper modification.

- Two fractions can be analyzed simultaneously. As a result, no extra delay is needed for the analysis of two product streams in one cycle.
- This system gives an accurate average concentration of each fraction collected.
- Conventional needle and arm injection arrangement in HPLC systems is replaced by a less expensive but faster mechanism.
- Analytical columns and UV detectors are selected in a way to yield the fastest possible analysis.

2.2.2 Principle of operation

The schematic diagram of the online monitoring system is given in Fig. 2.1 along with the process flow diagram. The principle of operation is explained here:

1. Since two fractions are collected as products, they are directed to two separate intermediate vials (VI1/VI2) with a certain operation time overlap.
2. The purging gas is inserted into the vial from lower port as soon as fraction collection starts and is shut off before fraction collection ends.
3. Then, sufficient time is given to ensure that the contents of vial are well mixed.
4. Once mixing is completed, the outlet valve (V2/V3) is opened and the contents are purged to the product bottle.
5. In the mean time as the contents of vial is being purged, the sampling valve (V4/V5) is switched to the load position. The valve loads a small sample of the stream in an injection loop (IL2/IL3) without any interruption in the flow of product.
6. Shortly after loading the sample, the sampling valve is switched back to the normal position (inject position). Subsequently, the product sample is injected into a stream of solvent and then will be resolved in the analytical column (C2/C3).
7. Fully-resolved peaks are analyzed by the UV detector (D2/D3). The calibration software converts the absorbance data to the concentration values.

The same procedure is repeated for the second fraction as soon as the controlling software decides on the next fraction collection. No delay is involved and two HPLC systems can operate in an independent manner.

It is worthy of attention that the contents of vials and tubings are purged by helium gas to reduce cross-contamination and the system is always filled with pressurized inert gas. Thus, the adverse effects of air penetration and solvent evaporation are minimized.

2.3 Experimental setup

2.3.1 Materials and equipment

Guaifenesin (referred as G) enantiomers, as a racemic mixture of (+)-G and (-)-G, were purchased from Fludan (Vankleek Hill, Canada). Chiral stationary phases (CSPs), Chiralcel OD and OD-H, were purchased from Daicel (Tokyo, Japan). These cellulose-based CSPs (cellulose tris (3,5-dimethylphenylcarbamate) coated on silica) are designed for high performance separations of enantiomers. The Chiralcel OD has a particle size of 20 μm , and that of Chiralcel OD-H is 5 μm . Chiralcel OD was used for preparative separation in a 10 $\times$ 1 cm prepacked column, and Chiralcel OD-H was used in two 15 $\times$ 0.46 cm columns for analysis in the online monitoring system.

Heptane and ethanol solvents were used as mobile phase from several suppliers. The composition of the mobile phase (heptane-ethanol) for both preparative work and analysis was 65:35 (v/v).

The HPLC modules, that is pumps, UV detectors, oven, and degassers were purchased from PerkinElmer (Shelton, USA). The switching valves were purchased from VICI (Schenkon, Switzerland).

2.3.2 Testing the intermediate vials

The target is to evaluate the mixing and cross-contamination in the vials. The basis of the test is checking the material balance through absorbance analysis. Any bi-ased deviation from mass balance or sporadic response is a sign of imperfect mixing. Cross-contamination can be readily detected by blank injections. We can relate the mass injected as feed to the concentration in the liquid holdup. Theoretically, the concentration in the vial liquid holdup is

$$c_H^t = \frac{c_T^F V_{inj}^F}{V_H} \quad (2.1)$$

where V_{inj}^F and V_H are the volume of the feed injected and the volume of the liquid holdup, respectively.

On the other hand, experimentally, the concentration in the vial liquid holdup is

$$c_H^e = \frac{A_S}{A_F} \frac{c_T^F V_{inj}^F}{V_{inj}^S} \quad (2.2)$$

where A_F and A_S are the areas under absorbance curves of the feed injected and sample taken from the liquid holdup, respectively. V_{inj}^S is the volume of the sample taken from the liquid holdup.

We define

$$\alpha = \frac{c_H^e}{c_H^t} \quad (2.3)$$

α must be unity for perfect mixing, and in case of blank injections, must be zero for no cross-contamination.

A typical case of analysis is given in Fig. 2.4. In this test, similar to normal operation, but without any HPLC column used, a pulse of feed is injected into the vial. Similar

to the procedure explained in Section 2.3.3, the vial is then pressurized and sufficient time is given until perfect mixing has achieved. Then a small sample of the vial contents is taken for analysis. This sample is directly injected into a similar stream of clean mobile phase and then analyzed using UV detector. Finally, α is found from experiments. The values of parameters involved in this test are given in Table 2.1. The α values are given in Table 2.2. Note that the last run is for a blank injection.

For majority of runs, α is very close to unity, which means, the measured concentration is a good representative of the average concentration. On the other hand, it is clear that there is minor cross-contamination between consecutive runs. However, if we inject a second blank, no peak can be identified within the sensitivity of the UV detector. This means that contamination is only carried to the next cycle. In other words, this monitoring system would have a dynamic with one cycle transient response until it gives accurate readings.

Figure 2.4: Testing mixing and cross-contamination in the intermediate vial. The mobile phase is heptane-ethanol (65:35, v/v). See Table 2.1 for the values of parameters. Note that the last peak is for a blank injection.

Table 2.1: Values of parameters involved in the vial test.

Parameter	Value
c_T^F	10 g/L
V_{inj}^F	50 μ L
V_{inj}^S	20 μ L
V_H	2 mL
ω	150 RPM

Table 2.2: The results of testing mixing and cross-contamination in the vial. Note that the last run is a blank injection.

Run	1	2	3	4	5	6	7	8	9	10
α	0.94	0.98	0.98	1.01	0.99	0.99	0.96	0.97	0.93	0.04

2.3.3 Design of human-machine interface

The human-machine interface (HMI) outlines are described here. The HMI software covers two important tasks of communicating with process components and interfacing

with user. National Instruments (www.ni.com) software and hardware products were used as the backbone of interfacing. LabVIEW development software package was used as the programming environment and various hardware products were used as input/output devices.

In order to minimize the development time, every part of the process equipment with input/output communication capabilities is programmed in a separate module, which can be cloned in a straightforward manner. Each HPLC pump and UV detector has an initialization state, manual mode, method mode, and shutdown state. Switching and solenoid valves do not have the method mode, but have other steps as of the pumps and detectors. In the method mode, data is logged to file from the pumps and detectors. Every module is designed with disable/enable capabilities so that it can be isolated from the rest of the code if necessary.

Although the programming was done in a modular way, a ‘main menu’ was designed for control and monitoring of the entire process components from single page as shown in Fig. 2.5. The process can be run through HMI in two modes: manual and automatic. In the manual mode, all modules can be accessed independently. The manual mode is the active mode at program startup to allow the operator to set the parameters including flow rate of pumps, wave length of detectors, etc. This mode is also designed to override the automatic mode in case of loss of control. As a result, at any time during the automatic mode, the HMI can be switched back to the manual mode to interrupt the process flow and make necessary changes.

Figure 2.5: A snapshot of the ‘main menu’ of the process HMI in the automatic mode of operation.

In the automatic mode, in the current version of HMI, the feed injection and fraction collection schemes are executed at steady state. These tasks involve valve sequencing and time planning. Provisions are made to add a model predictive control (MPC) scheme to the automatic mode of operation in the future.

The fraction collection task requires special attention because it is a constrained time scheduling problem with overlapped steps. The effluent stream leaving the process column is divided into four fractions as explained in Section 2.1.1. Every cut interval appears as a major step in fraction collection as follows:

- Fraction B
- Waste B+A
- Fraction A
- Tail waste

Only fraction B and fraction A are collected as products as mentioned earlier. Therefore, the online monitoring system is envisaged in a way to independently measure the average concentrations of these two fractions per every analysis/cycle. For this purpose, six minor steps are required for every fraction as follows:

- Filling-Gas on
- Filling-Gas off
- Sampling-Mixing
- Sampling-Pre-purging
- Sampling-Loading
- Sampling-Injecting

Overall, there are 17 time intervals to set and five time constraints, which reduce the degrees of freedom to 12 (see Figs. 2.6 and 2.7). The time constraints are applied through a novel application of property nodes of pointer slides and MathScript RT modules together (see for example Travis and Kring [46] for further details on programming terms). The fraction collection scheme is written in a MathScript node and the maximum range of pointer slides are set through their property nodes in combination together and in accordance with the time constraints implemented in the MathScript node. For example, ‘Filling-Gas on’ minor step must be capped at the value of the fraction time interval (A or B). Therefore, the upper limit of the pointer slide of ‘Gas on’ minor step is automatically adjusted with the fraction time interval (see Fig. 2.7).

Figure 2.6: Implementation of the fraction collection scheme.

Regarding the safety issues, a shutdown procedure is devised for normal or emergency interruption of the process. After the shutdown button is pressed, a stop command is sent to all devices, which forces modules out of their manual/method mode and then shutdown procedures are executed. The shutdown procedures may include putting devices in their default settings, closing data logging files, and terminating serial communications. The HMI will not exit the run mode until all devices report back the accomplishment of their shutdown procedures.

Figure 2.7: Implementation of time constraints arising in the fraction collection scheme.

2.4 Interim conclusion

In this chapter, after a brief comparison of the available processes, we described the ISCC process in technical terms. We also showed how the online monitoring system proposed in this work is different from available instruments. We elaborated on the importance of mixing in the intermediate vials and confirmed that in practice, this system is viable. We have run the process qualitatively to ensure that all sections can operate seamlessly. Experimental implementation of the optimization results discussed in Chapter 5 and also the model predictive control scheme discussed in Chapter 6 would be the subjects of future work.

Several factors need careful attention when implementing the process design and on-line monitoring system: Partial loop filling may be a major source of irreproducibility. This can be avoided by using a loop volume much larger than injection volume and synchronization of software, pump, and switching valve to ensure loading of accurate amount of feed.

Tubes with smaller diameter are favored for injection loop to minimize axial dispersion during injection and achieve ideal rectangle form of feed delivery. Axial dispersion in the injection system causes long tails in the elution profile resulting in poor resolution. However, pressure drop limits the smallest diameter that can be used for this purpose.

Proper mixing in the intermediate vials is essential for online monitoring of the products' concentration profiles. For large molecules or for viscous fluids, mixing must be enhanced. In general, vial volume, gas inlet pressure, mixing time, and shaker speed should be adjusted to achieve proper mixing. Use of a transparent material for the vials allows visual inspection of the mixing patterns.

A short measurement time for the effluent concentration values is necessary for high frequency feedback information to the controller. This is however, dictated by the maximum allowable pressure drop of the stationary phase of the analytical column. Selection of the column length, stationary phase, and eluent flow rate should be such that analysis time is minimized along with base line separation with some room for flexibility to account for process variations.

Nomenclature

A_F	area under feed absorbance peak [mAU.s]
A_S	area under sample absorbance peak [mAU.s]
c_H	average concentration in the vial liquid holdup [g/L]
c_T^F	total feed concentration [g/L]
V_{inj}^F	feed injection volume [μ L]
V_{inj}^S	sample injection volume [μ L]
V_H	volume of vial liquid holdup [μ L]

Greek letters

α	parameter defined in Eq. 2.3 [-]
ω	shaker speed [RPM]

Subscripts and superscripts

A	more retained component (S)-(+)-guaifenesin
B	less retained component (R)-(-)-guaifenesin
e	experimental
F	feed
H	holdup
inj	injection
S	sample
t	theoretical

Chapter 3

Modeling and Numerical Solution Methods

A model is a simplified mathematical representation of a physical phenomenon. The aim of devising a model in general is to investigate and acquire a better insight into a problem, which was otherwise hard to obtain directly through experiments. However, care must be taken that every model has a certain range of validity and besides, in many practical applications, it relies on experimental data to some extent. In the field of chemical engineering, modeling starts from a ‘balance’ equation, which implies that mass, energy, and momentum are conserved in normal conditions.

First-principle models hinge on one of the balance equations, and typically reduce to algebraic equations in the end. However, depending on the dimensions of the problem, the effect of time, and the solution technique utilized, we may face solving differential equations in some steps, which is the main point of argument in this chapter.

In chromatography, adsorbate partitions between a mobile and a stationary phase. This partitioning is in fact the cause of separation as it directly affects the velocity of the adsorbate concentration front, which takes place due to a variety of reasons such as different molecular interactions, size exclusion, etc. Thermodynamics usually describes the equilibrium between two phases, which is described using an adsorption isotherm.

Adsorption thermodynamics and transport phenomena are vast fields of research. For practical applications like ours, it is customary to assume one or more types of isotherms and try to fit experimental data to the prevailing theory. In this work, we rely on the experimental data available in the literature and focus on the modeling and simulation aspects.

In chromatographic adsorption, time-varying, one-dimensional material balance which is the backbone of any formulation, appears as one or a set of partial differential equations (PDEs) in the Cartesian coordinates¹. If detailed intra-particle mass transfer effects are also included, another set of differential equations may arise, which must be solved simultaneously in the spherical coordinates.

For majority of the chromatographic models that accounts for realistic process phenomena such as axial dispersion and mass transfer limitation, there is no analytical solution available, and we need to resort to numerical methods. Handling flux terms

¹In fact, a true moving bed (TMB) process can be called an exception as it is considered a stationary process without temporal variations.

is of practical importance in numerical solution of PDEs, which appear in chromatography as flux approximation heavily contributes to the overall accuracy of modeling. In this chapter, after a brief review of various numerical methods, we identify the best numerical schemes in terms of accuracy and speed, which will be used later for multi-objective optimization and control applications.

3.1 Overview of modeling approaches

We assume that the chromatographic bed is a cylindrical conduit, and we consider variations only in the z direction. Therefore, the model equations can be written in the Cartesian coordinates. For a control volume of $\Delta V = A\Delta z$, we can write the time-dependent, one-dimensional material balance as

$$\varepsilon \int_V \frac{\partial c_i}{\partial t} dV + (1-\varepsilon) \int_V \frac{\partial n_i}{\partial t} dV = \varepsilon A \left[v c_i - D_{ax,i} \frac{\partial c_i}{\partial z} \right]_z - \varepsilon A \left[v c_i - D_{ax,i} \frac{\partial c_i}{\partial z} \right]_{z+\Delta z} \quad (3.1)$$

where c_i and n_i are the concentrations of the component i in the fluid phase and in the stationary phase, respectively. v is the interstitial velocity and $D_{ax,i}$ is the axial dispersion of the component i . ε is the overall void fraction of column.

Assuming that c_i and n_i can be taken constant in the control volume, and then simplifying the right-hand side of Eq. 3.1 gives

$$\frac{\partial c_i}{\partial t} + \frac{(1-\varepsilon)}{\varepsilon} \frac{\partial n_i}{\partial t} = \frac{[v c_i - D_{ax,i} \frac{\partial c_i}{\partial z}]_z - [v c_i - D_{ax,i} \frac{\partial c_i}{\partial z}]_{z+\Delta z}}{\Delta z} \quad (3.2)$$

Finally, after writing this difference equation in the differential form, we obtain

$$\frac{\partial c_i}{\partial t} + \frac{(1-\varepsilon)}{\varepsilon} \frac{\partial n_i}{\partial t} + \frac{\partial (v c_i)}{\partial z} = D_{ax,i} \frac{\partial^2 c_i}{\partial z^2} \quad (3.3)$$

3.1.1 General rate model

We have yet to clarify how n_i is related to c_i . In fact, many of the modeling techniques are named based on the way this relation is defined. The general rate model (GRM) [5] is the most detailed one, which considers radial distribution of the concentration of adsorbate in stationary phase

$$\varepsilon_p \frac{\partial c_{p,i}}{\partial t} + (1-\varepsilon_p) \frac{\partial n_{p,i}}{\partial t} = D_{eff,i} \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial c_{p,i}}{\partial r} \right) \quad (3.4)$$

and then Eq. 3.3 has to be written as a function of the mass transfer rate, which is in turn a function of adsorbate concentration at the surface of particles

$$\frac{\partial c_i}{\partial t} + \frac{(1-\varepsilon_e)}{\varepsilon_e} k_{ext,i} a_p [c_i - c_{p,i}(r = R_p)] + \frac{\partial (v c_i)}{\partial z} = D_{ax,i} \frac{\partial^2 c_i}{\partial z^2} \quad (3.5)$$

In these equations

- a_p is the external surface area of solid particles,
- $c_{p,i}$ is the intra-particle concentration in pores,
- $k_{ext,i}$ is fluid to particle mass transfer coefficient,
- $n_{p,i}$ is the concentration in solid phase,
- $D_{eff,i}$ is the pore diffusion coefficient,
- ε_e is the external void fraction of column,
- ε_p is the internal void fraction of solid particles.

3.1.2 Linear driving force models

GRM has been simplified in several aspects; mass transfer between fluid and stationary phases can be explained by a linear driving force as [47]

$$\frac{\partial n_i}{\partial t} = k_s (n_i^* - n_i) \quad (3.6)$$

or similarly [5]

$$\frac{\partial n_i}{\partial t} = k_l (c_i - c_i^*) \quad (3.7)$$

The former one is called solid film driving force model, and the latter is liquid film driving force model. n_i^* is the equilibrium concentration in solid phase with respect to that of fluid phase c_i . Similarly, c_i^* is the equilibrium concentration in the fluid phase with respect to that of solid phase n_i . Care must be taken that Eqs. 3.6 and 3.7 may not necessarily give the same results [5]. In general, Eq. 3.6 is accurate when the solid film is the controlling step of mass transfer, and Eq. 3.7 is accurate when the liquid film is the controlling step.

3.1.3 Equilibrium dispersive model

If the mass transfer resistance is negligible, we can further simplify Eq. 3.3, and assume that n_i is in constant equilibrium with c_i . Hence, we obtain the equilibrium dispersive model which is very similar to Eq. 3.3 in appearance, but it carries an auxiliary equation, which is in fact the adsorption isotherm

$$n_i = f_i(c) \quad (3.8)$$

3.1.4 Ideal model of chromatography

Finally, if axial dispersion in the fluid phase is also neglected, we obtain the ideal model of chromatography

$$\frac{\partial c_i}{\partial t} + \frac{(1 - \varepsilon)}{\varepsilon} \frac{\partial n_i}{\partial t} + \frac{\partial (vc_i)}{\partial z} = 0 \quad (3.9)$$

This is referred to as equilibrium theory model by some researchers [29]. Despite its simplicity, it has been the subject of ongoing research for several decades [11, 48, 49, 50]

3.1.5 Initial and boundary conditions

Here we only describe the boundary conditions for the linear driving force and ideal models because we widely use these models throughout our work. As we usually start the operation from a clean column state, the initial condition is zero concentration of adsorbate in the fluid and solid phase

$$c_i(0, z) = 0, \quad n_i(0, z) = 0 \quad (3.10)$$

The only exception is the cyclic injections in Chapters 5 and 6. In that case, the initial condition of one cycle is the final condition of the previous cycle.

In general, we utilize the Danckwerts' boundary conditions at the inlet and outlet of column. For inlet, we have

$$D_{ax} \frac{\partial c_i(t, 0^+)}{\partial z} = v(c_i(t, 0^+) - c_{i,in}(t)) \quad (3.11)$$

and for outlet

$$\frac{\partial c_i(t, L)}{\partial z} = 0 \quad (3.12)$$

For the ideal model, the boundary conditions boil down to

$$c_i(t, 0) = c_{i,in}(t) \quad (3.13)$$

These equations must be converted to their discretized forms to be used with numerical methods discussed in this chapter.

3.2 Adsorption isotherms

3.2.1 Linear isotherm

The equilibrium between c_i and n_i is described by an adsorption isotherm in general. This is valid as long as kinetic effects can be neglected. The simplest form which is derived from the thermodynamic Henry's law, linearly relates the solid and fluid phase concentrations together

$$n_i = H_i c_i \quad (3.14)$$

It is apparent that there is a one-to-one effect of components for this linear isotherm. In other words, no competition is considered over adsorption sites. This is a good approximation for low concentrations, but it might drastically be violated at elevated concentrations.

3.2.2 Langmuir isotherm

In contrast to linear isotherm, a competitive Langmuir isotherm not only does take into account the competition, it also assumes a finite number of sites available for competition. The general competitive Langmuir isotherm can be written as

$$n_i = \frac{q_s K_i c_i}{1 + \sum_{i=1}^{N_c} p_i K_i c_i} \quad (3.15)$$

q_s is the saturation capacity of the adsorbent and K_i is the equilibrium constant of adsorption for component i . p_i is the parameter that shows the type of competition, and can only take 1 and -1 values. For a binary system, four types of Langmuir isotherms can be obtained [49]. The classical competitive Langmuir isotherm is obtained for $p_1 = 1$ and $p_2 = 1$. For simplicity, we drop these parameters from our formulations because only this type of isotherm is discussed in this work.

Moreover, it is customary to write the Langmuir isotherm in a different way with defining $H_i = q_s K_i$

$$n_i = \frac{H_i c_i}{1 + \sum_{i=1}^{N_c} K_i c_i} \quad (3.16)$$

3.3 General assumptions

Here are the general assumptions we have assumed in this work. More details will be given upon establishing the problems in the next chapters:

- Kinetic adsorption effects are neglected.
- System is considered isothermal in all directions.
- Non-ideal thermodynamic effects (e.g., heat of adsorption) are neglected.
- The effects of pressure drop (e.g., liquid or bed compressibility) are neglected.

3.4 Overview of numerical methods

There are problem-specific difficulties regarding the simulation of chromatographic systems. Sharp fronts are likely to occur in many circumstances, such as when the column is very efficient [51] or when the isotherm is of Langmuir type (self-sharpening effect). When no analytical solutions exist for the governing equations, which is most often the case, effective numerical methods must be sought to guarantee accuracy, stability, and speed in handling sharp fronts. It has been shown that conventional numerical methods, such as ordinary finite-difference (FD), are not capable of capturing the true effects of sharp fronts efficiently [52]. As an alternative, the use of more accurate techniques, such as finite-element (FE) and its variants such as orthogonal collocation on finite elements (OCFE), have been reported in the literature [53]. However, the FE method is computationally expensive and this undesirable feature renders it inconvenient for many applications.

A schematic diagram of steps involved in the three main numerical solution techniques, namely finite-volume (FV), finite-difference (FD) and finite-element (FE) methods is given in Fig. 3.1. All of these techniques start from an integral form of the material balance. Subsequently, both FD and FE methods require that the integral form of the material balance be converted into a differential form, but in the FV method, the flux terms are approximated and replaced directly in the integral form of the model equation. In the FD method, some or all of the derivative terms have to be converted to the approximated difference terms. In the FE method, the solution is approximated in the form of simple functions. The numerical approximation error is minimized by minimizing the residual terms, which is partly an optimization problem. The high accuracy of the FE method originates from this step, and because there is no similar error-minimization step in the FV method, it becomes less accurate than the FE method. However, error minimization and handling of large matrices, which are almost inevitable in the FE method, require long CPU time and large memory.

The final step of the solution is similar in all methods: depending on the mode of discretization, it comprises the solution of a set of ordinary differential equations (ODEs) or algebraic equations.

Flux estimation techniques have been the traditional approach to resolving discontinuities and sharp fronts [54, 55]. Since the FV method carries the physical notion of flux, different flux estimation techniques can be readily applied to the FV method. Flux estimation techniques can also be applied to the FD method with necessary modifications as shown in Fig. 3.1. However, fewer steps are needed in the FV-based solution techniques. Therefore, for conceptual convenience and ease of implementation, the FV method is preferred over the FD method for the majority of applications. Nonetheless, in the FV method, the demand of accuracy and stability can be met simultaneously neither with ordinary low-order schemes such as upwind differencing scheme (UDS) nor with high-order unbounded ones, such as central differencing scheme (CDS) [56]. As a general rule, low-order schemes cause extreme smoothing, whereas unbounded high-order schemes might cause unrealistic oscillations. To resolve these issues, the class of total variation diminishing (TVD) schemes, first introduced by Harten [57] was designed for accurate oscillation-free solutions. These schemes were initially developed to address the smoothing and unrealistic oscillations that occurred in the time-dependent gas dynamics problems. Later, many other researchers contributed to the development of currently available TVD schemes [58, 59, 60]. The fundamentals of TVD schemes are briefly described in Section 3.6 focusing on chromatographic systems.

In this chapter, a class of high-resolution central schemes [25] in conjunction with TVD flux limiters has been implemented for the simulation of chromatographic adsorption processes. The equilibrium theory model and the equilibrium-dispersive model with mass-transfer resistance were considered separately as two case studies. The performance of flux limiters was tested to identify the best choice for solving chromatographic model equations. The results are reported for elution under both linear and nonlinear conditions. The results of UDS, which particularly in this case, is equivalent to the ubiquitous FD method were included as an indication of the lowest level of accuracy. For the equilibrium theory model, analytical solutions are available. Thus, they were readily used as an indication of the best possible level of accuracy. However, at the presence of axial dispersion and mass-transfer effects, the OCFE method was used to indicate the best possible level of accuracy.

As an addition to our original work published earlier [61], we briefly review the weighted essentially non-oscillatory (WENO) schemes here as well, as they have recently been found to be competitive rivals in similar fields of research [26, 62]. These schemes have a lot to share with essentially non-oscillatory (ENO) schemes [63], but they have better performance in many practical applications.

3.5 Modeling

The model equation describing a chromatographic system under equilibrium theory assumptions, that is no axial dispersion and no mass-transfer resistance is given by Eq. 3.9. The initial and boundary conditions are given by Eqs. 3.10 and 3.13. Under these assumptions, an analytical solution is available only for certain conditions [11]. On the other hand, this partial differential equation can admit weak solutions, that is solutions which contain discontinuities [5]. Therefore, efficient numerical methods

Figure 3.1: Comparison of the steps involved in the application of the finite difference (FD), finite element (FE), and finite volume (FV) methods.

are required to obtain accurate, stable, and fast results when no analytical solution is available [64].

When axial dispersion and mass-transfer resistances are included, the system can be described by the linear driving force model (Eqs. 3.3 and 3.7).

The initial conditions for these equations are the same as for Eq. 3.9, but the Danckwerts' boundary conditions apply at the inlet and outlet as given in Eqs. 3.11 and 3.12.

The equilibrium relationships between fluid phase and solid phase are given under linear and nonlinear chromatographic conditions by Eqs. 3.14 and 3.16, respectively.

3.6 Solution method

In this section, we first describe the solution method by elaborating on the FV approach for a transient, one-dimensional problem. Then, the principles of total varia-

tion diminishing (TVD) central schemes and accompanying flux limiters are presented. Subsequently, the approach is extended to the chromatographic model equations.

Figure 3.2: Implementation of the conservation law over a fixed control volume.

As illustrated in Fig. 3.2, applying the conservation law over a fixed control volume (cell) gives

$$\int_V \frac{\partial y}{\partial t} dV = - \int_S F \cdot n dS + \int_V S_G dV \quad (3.17)$$

Here, y is any conserved quantity, and S_G represents a source term, which can be a function of t , z , and y . F is the flux term including both convective and diffusive parts

$$F = f + J \quad (3.18)$$

where f is the convective part and J is the diffusive part.

y and S_G can be taken outside of the integrals as the cell-averaged values

$$\frac{\partial y}{\partial t} \int_V dV = - \int_S F \cdot n dS + S_G \int_V dV \quad (3.19)$$

For any cell j with a constant cross-sectional area A , Eq. 3.19 can be written as

$$\frac{\partial y_j}{\partial t} \int_V dV = A(F_{j-1/2} - F_{j+1/2}) + S_G \int_V dV \quad (3.20)$$

Finally, in semi-discrete form, it can be written as

$$\frac{\partial y_j}{\partial t} = \frac{1}{\Delta z} (F_{j-1/2} - F_{j+1/2}) + S_G \quad (3.21)$$

In this formulation, the conserved quantity and source term are cell-averaged values, but flux terms must be obtained at cell walls, which for a one-dimensional problem, are designated by $j - 1/2$ for upstream and by $j + 1/2$ for downstream cell walls. The advantage of high-resolution numerical schemes is a precise interpolation between cell averages to cell walls with the aim of reconstructing these flux terms in such a way that accuracy and stability are maintained as much as possible. It is important to note that the primary focus must be given to the convective flux term, because it is usually the most difficult part to address in flow systems. Hence, we start from a pure convective system, and then, we add the diffusive part to the formulation.

3.6.1 TVD schemes

In order to elucidate the problem, here, we first elaborate on the extrapolation of convective part of flux terms. Let us start from very simple, but well-known formulations, UDS and CDS. In UDS, we have

$$f_{j-1/2} = f_{j-1}, \quad f_{j+1/2} = f_j \quad (3.22)$$

Referring to Fig. 3.2, f_{j-1} and f_j are flux terms calculated from cell-averaged values at cells $j - 1$ and j , respectively. This formulation is of first-order accuracy, but it offers non-oscillatory results. On the other hand, CDS is a linear approximation of flux terms at cell walls, which, for a uniform grid spacing, becomes [56]

$$f_{j-1/2} = \frac{1}{2}(f_{j-1} + f_j), \quad f_{j+1/2} = \frac{1}{2}(f_j + f_{j+1}) \quad (3.23)$$

Despite its simplicity, CDS offers second-order accuracy [56], which is remarkable compared to UDS. However, it can be proved that classical second-order schemes like CDS are inevitably oscillatory [58].

The low-order accuracy of UDS and the instability of CDS are obstacles in resolving sharp fronts efficiently. Harten [57] suggested that the criterion for obtaining non-oscillatory results is that the total variations (TV) must diminish over time in the solution domain, which, for a transient, one-dimensional, scalar problem, is defined as

$$TV(y^n) = \sum_{j=1}^{N_z-1} \Delta y_j^n = \sum_{j=1}^{N_z-1} (y_{j+1}^n - y_j^n) \quad (3.24)$$

This criterion can be formulated as

$$TV(y^{n+1}) \leq TV(y^n) \quad (3.25)$$

where n is the index of time discretization.

Qualitatively, in the TVD schemes, the monotonicity is preserved; i.e. the number of extrema (minimum or maximum) does not increase over time. Furthermore, the magnitudes of these extrema are not accentuated over time [56].

3.6.2 Flux limiters

Harten [57] gave a set of necessary and sufficient conditions in the form of constraints for numerical schemes to be TVD. However, these conditions are not convenient in practice, since they cannot be cast in a simple universal format. Therefore, several researchers have reformulated these conditions over time [58, 59, 60]. In this chapter, our approach is based on the classification and extension of high-resolution, TVD schemes made by Sweby [58]. He introduced the concept of flux limiters, $\phi(r_j)$, functions that guarantee TVD compliance by regulating the slope of variations. Apart from his own contribution, he also incorporated several other researchers' approach into his ready-made, single-variable format of flux limiters. Here, we briefly explain their properties and principles of operation.

Sweby [58] proposed his notion of flux limiter as a sole function of consecutive gradients

$$r_j = \frac{y_j - y_{j-1}}{y_{j+1} - y_j} \quad (3.26)$$

Figure 3.3: Region of second-order, TVD flux limiters (shaded area) [58].

The flux limiter, $\phi(r_j)$, is designed to fall in a constrained region when it is plotted versus r_j . This region of second-order, TVD flux limiters is shown in Fig. 3.3 by the shaded area, which is obtained by enforcing the set of constraints imposed on the variation of flux terms to guarantee both stability and second-order accuracy. Further details can be found in the literature [57, 58, 64].

A well-known approach is to combine low-order (f^{Low}) and high-order (f^{High}) flux approximation techniques by means of a suitable flux limiter

$$f = f^{Low} + \phi(r_j)(f^{High} - f^{Low}) \quad (3.27)$$

For instance, if we take f^{Low} as UDS and f^{High} as CDS, one can recover these schemes by letting $\phi(r_j)$ to be equal to 0 and 1, respectively. Obviously, these values do not comply with the second-order, TVD restrictions as shown in Fig. 3.3. Hence, neither of these schemes is second-order TVD.

3.6.3 Class of high-resolution central schemes

Flux limiters can be used with variety of numerical schemes. Sweby [58] has discussed a few of them, but here, we prefer to use the class of high-resolution central schemes of Kurganov and Tadmor [25] as it offers higher accuracy with respect to simple upwind scheme (UDS) and many other high-resolution schemes. Besides, it can be implemented in both fully discrete and semi-discrete ways. We have adopted semi-discretization, because it can be readily coupled to general-purpose or proprietary ODE solvers.

For the convective flux, Kurganov and Tadmor [25] suggested

$$f_{j-1/2} = \frac{1}{2} \{ f(y_{j-1/2}^R) + f(y_{j-1/2}^L) - a_{j-1/2} [y_{j-1/2}^R - y_{j-1/2}^L] \} \quad (3.28)$$

$$f_{j+1/2} = \frac{1}{2} \{ f(y_{j+1/2}^R) + f(y_{j+1/2}^L) - a_{j+1/2} [y_{j+1/2}^R - y_{j+1/2}^L] \} \quad (3.29)$$

where

$$y_{j-1/2}^L = y_{j-1} + 0.5\phi(r_{j-1})(y_j - y_{j-1}), \quad y_{j-1/2}^R = y_j - 0.5\phi(r_j)(y_{j+1} - y_j) \quad (3.30)$$

$$y_{j+1/2}^L = y_j + 0.5\phi(r_j)(y_{j+1} - y_j), \quad y_{j+1/2}^R = y_{j+1} - 0.5\phi(r_{j+1})(y_{j+2} - y_{j+1}) \quad (3.31)$$

where L and R superscripts represent left-hand side and right-hand side of each cell wall, respectively. $a_{j\pm 1/2}$ is defined as maximal local propagation speed, and it is the maximum absolute value of the eigenvalues of the Jacobian of f [25, 64].

For convection–diffusion problems, Kurganov and Tadmor [25] suggest incorporating the following term for the diffusive flux, which can handle the dispersion in a straightforward manner

$$J_{j+1/2} = \frac{1}{2} \left[J(y_j, \frac{y_{j+1} - y_j}{\Delta z}) + J(y_{j+1}, \frac{y_{j+1} - y_j}{\Delta z}) \right] \quad (3.32)$$

3.6.4 WENO schemes

The backbone of ENO and WENO schemes is precise interpolation between cell-average values in order to obtain high-order accuracy and, at the same time, to prevent spurious oscillations. In ENO schemes, a group of cells called a stencil is selected among several candidates for reconstruction in such a way that the choice gives the smoothest result in some sense. On the other hand, in WENO schemes, a convex combination of all the candidate stencils is applied [62]. This approach simply has important implications in practice. The ENO schemes necessitate using conditional expressions in programming, which are both nonlinear and CPU intensive, while the WENO schemes are smooth in this sense. We must emphasize that they are also simpler in implementation than many TVD schemes, but their smoothness may result in higher numerical dispersion.

We have used the following third-order WENO scheme [26, 65]

$$f_{j+1/2} = \omega_0 f_{j+1/2}^0 + \omega_1 f_{j+1/2}^1 \quad (3.33)$$

where

$$f_{j+1/2}^0 = \frac{1}{2} (f(y_{j+1}) + f(y_j)) \quad (3.34)$$

and

$$f_{j+1/2}^1 = \frac{3}{2} f(y_j) - \frac{1}{2} f(y_{j-1}) \quad (3.35)$$

The weight factors ω_j are defined as

$$\omega_j = \frac{\alpha_j}{\alpha_0 + \alpha_1} \quad (3.36)$$

where

$$\alpha_j = \frac{d_j}{(\epsilon + \beta_j)^2} \quad (3.37)$$

ϵ is a very small positive value (here 1×10^{-6}) added to avoid division by zero.

β_j s are the smoothness indicators, and defined as

$$\beta_0 = (f(y_{j+1}) - f(y_j))^2, \quad \beta_1 = (f(y_j) - f(y_{j-1}))^2 \quad (3.38)$$

and $d_0 = 2/3$ and $d_1 = 1/3$.

3.6.5 Application of the TVD schemes to chromatography

The general form of solution technique discussed in Section 3.6.3 is here applied to the chromatographic model equations as follows

$$\frac{\partial c_j}{\partial t} = \frac{1}{\Delta z}(F_{j-1/2} - F_{j+1/2}) - \frac{1-\varepsilon}{\varepsilon} \frac{\partial n_j}{\partial t} \quad (3.39)$$

where the component index, i , is dropped for simplicity, since the equation is for a single-component system.

For equilibrium theory model, Eq. 3.39 can be further simplified for any isotherm as

$$n = n(c) \quad (3.40)$$

Therefore

$$\frac{\partial n_j}{\partial t} = \frac{\partial n}{\partial c} \frac{\partial c_j}{\partial t} = n'(c) \frac{\partial c_j}{\partial t} \quad (3.41)$$

Substituting in Eq. 3.39 yields

$$\frac{\partial c_j}{\partial t} = \frac{1}{\Delta z}(F_{j-1/2} - F_{j+1/2}) - \frac{1-\varepsilon}{\varepsilon} n'(c) \frac{\partial c_j}{\partial t} \quad (3.42)$$

Further rearrangement gives

$$\left(1 + \frac{1-\varepsilon}{\varepsilon} n'(c)\right) \frac{\partial c_j}{\partial t} = \frac{1}{\Delta z}(F_{j-1/2} - F_{j+1/2}) \quad (3.43)$$

In fact, the leftmost term on the left-hand side of this equation can be called a capacity function [64]. It is a constant for linear isotherm and a function of concentration for other types of isotherms. Further discussions about these equations can be found in Appendix B.

We can divide both sides of Eq. 3.43 by the capacity function

$$\frac{\partial c_j}{\partial t} = \frac{1}{\Delta z(1 + \frac{1-\varepsilon}{\varepsilon} n'(c))}(F_{j-1/2} - F_{j+1/2}) \quad (3.44)$$

3.44 can be integrated using any standard ODE solver.

Although Eq. 3.43 resembles a quasilinear PDE, it is still in the original conservation form and with proper manipulation, it can satisfy the entropy condition [64]. However, it is beyond the scope of this work to analyze the numerical form of entropy condition to prove that a correct weak solution is obtained. Instead, we investigate the convergence of solutions by comparing them with analytical solutions as explained in Section 3.7.

In chromatography, the convective part of flux is

$$f(c, v) = vc \quad (3.45)$$

Apart from this, we need the maximal local propagation speed, $a_{j\pm 1/2}$, for Eqs. 3.28 and 3.29 to construct the high-resolution numerical flux. At first glance, it seems that the chromatographic band propagation speed, which is the slope of characteristics must be considered for this purpose. However, since in chromatography, the linear velocity is always greater than the band propagation speed, it must be used as the maximal local propagation speed. Further details regarding the propagation speed

and Courant–Friedrichs–Lewy (CFL) condition are given in Appendices C and D, respectively. In liquid chromatography, the linear velocity is assumed constant [5]. Therefore, in Eqs. 3.28 and 3.29, $a_{j\pm 1/2} = v$, which is a constant. Consequently, after substituting the respective terms and simplifying Eqs. 3.28 and 3.29, we obtain

$$f_{j-1/2} = v [c_{j-1} + 0.5\phi(r_{j-1})(c_j - c_{j-1})], \quad f_{j+1/2} = v [c_j + 0.5\phi(r_j)(c_{j+1} - c_j)] \quad (3.46)$$

For the detailed model (i.e., with axial dispersion and mass-transfer resistance), Eq. 3.39 can be readily employed along with Eq. 3.7, which defines the source term. No further treatment is necessary.

The diffusive flux is given by

$$J = -D_{ax} \frac{\partial c}{\partial z} \quad (3.47)$$

It can be inferred from Eq. 3.32 that this will be reduced to the following discretized formulas if the dispersion coefficient is assumed constant

$$J_{j-1/2} = -D_{ax} \frac{c_j - c_{j-1}}{\Delta z}, \quad J_{j+1/2} = -D_{ax} \frac{c_{j+1} - c_j}{\Delta z} \quad (3.48)$$

As shown above, the FV approach can be readily extended to the chromatographic model equations, but care must be taken, because the formal proof of stability is given when capacity functions and source terms are absent. Actually, for the system of equations like what arises in binary chromatographic separation, the formal proof is even harder to establish [25] (results are not given in this chapter). Later, we will show through simulation results that for this problem, the above mentioned add-ons can be handled satisfactorily. In this work, we do not cover higher-order treatment of capacity functions and source terms, which can be a topic of further research.

We have used variable-step ODE solver, ode45, from MATLAB for integration, which is based on Runge–Kutta (4,5) formula, the Dormand–Prince pair. This solver can regulate the size of time steps efficiently for nonstiff problems. As a result, the size of time step is not fixed. The above set of semi-discretized equations was integrated on an Intel T2450, 2.0 GHz CPU and 1 GB memory. For OCFE method, ASPEN Chromatography package was used with 400 elements and 7 internal points.

3.6.6 Application of the WENO scheme to chromatography

The application of the third-order WENO scheme is very similar to what explained in Section 3.6.5. The same manipulations are required and all the discretized formulas are valid. However, the convective flux terms $f_{j-1/2}$ and $f_{j+1/2}$ must be reconstructed via Eq. 3.33 accordingly. The diffusive flux terms must be treated exactly as given in Section 3.6.5.

Care must be taken that a general condition must hold for applying this WENO scheme

$$f'(c, v) \geq 0 \quad (3.49)$$

We have used the same ODE solver for WENO schemes, but a different computer for running the simulations because we added this part of the investigations later. The comparisons were made on an Intel Core i5-2430M, 2.40 GHz CPU and 3 GB memory on a 32bit operating system.

3.7 Results and discussion

We present here the results of two case studies: Case A was modeled by the equilibrium theory, which is theoretically a chromatographic column with infinite efficiency. In case B, axial dispersion and mass-transfer resistance were also included, resembling a more realistic column with finite efficiency. We consider case study A as a pure convection (advection) problem and case study B as a convection–diffusion problem in accordance with the formulations given in Kurganov and Tadmor [25]. As summarized in Table 3.1, the two case studies were simulated under linear and Langmuir chromatographic conditions. The injections were chosen as pulse and step inputs. The simulation data taken from the literature [66, 67, 68] are presented in Table 3.2. The number of grid points was fixed at 400 for Figs. 3.4, 3.5, 3.7, 3.8 and 3.10.

There are about a dozen TVD flux limiters reported in the literature. For brevity, in this work, we investigated the performance of only a representative set of them, which are given in Table 3.3. Among the selected flux limiters, van Leer, MC, superbee, and minmod are symmetric, but Koren is asymmetric based on the symmetry property defined by Sweby [58]

$$\frac{\phi(r_j)}{r_j} = \phi\left(\frac{1}{r_j}\right) \quad (3.50)$$

Table 3.1: Summary of conditions considered in the case studies.

Case study	Model	Input	Isotherm	Figure number
Case A	Equilibrium theory	Pulse	Linear Langmuir	3.4(a) 3.4(b)
		Step	Linear Langmuir	3.5(a) 3.5(b)
Case B	Equilibrium-dispersive with mass-transfer resistance	Pulse	Linear Langmuir	3.7(a) 3.7(b)
		Step	Linear Langmuir	3.8(a) 3.8(b)

Table 3.2: Simulation parameters [66, 67, 68].

Parameter	Case A	Case B
L (cm)	25	25
D (mm)	4	4
Q (mL/min)	1	1
v (cm/s)	0.188	0.188
c_F (g/L)	15	15
c_{ref} (g/L)	15	15
ε	0.704	0.704
V_{inj} (μ L)	20	20
H_A	3.49	3.49
K_A (L/g)	0.055	0.055
D_{ax} (cm ² /s)	NA	1.31×10^{-3}
Pe	∞	3583.9
k_l (1/s)	NA	18.3

Table 3.3: Flux limiters investigated in this study.

Flux limiter	Formula
van Leer [55]	$\phi(r) = (r + r) / (1 + r)$
MC [69]	$\phi(r) = \max [0, \min (2r, 0.5(1 + r), 2)]$
superbee [70]	$\phi(r) = \max [0, \min (2r, 1), \min (r, 2)]$
minmod[70]	$\phi(r) = \max [0, \min (1, r)]$
Koren [71]	$\phi(r) = \max [0, \min (2r, (1 + 2r) / 3, 2)]$

We emphasize that flux limiters are different in terms of the accuracy they provide, the computational time they need, and the asymmetric properties they exhibit. These can be problem-specific in general. Therefore, there is a need to evaluate the performance of the TVD flux limiters for chromatographic separation processes.

We analyzed both exit and axial concentration profiles for single-component injections to evaluate the accuracy, stability, and computational (CPU) time of the numerical solutions under different conditions. For visual inspection, exit concentration profiles were investigated for fixed number of grid points as summarized in Table 3.1 and illustrated in Figs. 3.4, 3.5, 3.7, and 3.8. Smoothing, which is caused by numerical dispersion, is the usual measure of accuracy. The results of the UDS and analytical solutions (or OCFE where analytical solutions were not available) were also included for comparison as a measure of the lower and upper limits of accuracy, respectively. It is worthy of attention that for uniform grid spacing, UDS on the FV method is equivalent to the ubiquitous FD method.

The stability of the numerical schemes is determined by the absence of spurious oscillations in all domains of solution, which can be visually inspected. Moreover, we particularly took note of asymmetric and oversharpening effects of flux limiters as additional measures of accuracy, since they can be detrimental to the simulation of chromatographic model equations. Some of the conditions considered in the case studies (e.g., pulse input and linear isotherm in case study A) ideally produce symmetric profiles and thus can be used for visual analysis of symmetry. On the other hand, Langmuir isotherm was used to evaluate the performance of the flux limiters in resolving combination of simple waves and sharp fronts. Regarding oversharpening effects, because there is no clear measure of oversharpening in the literature, we have assumed that the analytical solutions and OCFE are accurate enough to be used as reference. Therefore, should a flux limiter deliver results which are sharper than those of the reference solutions, we reported it as inaccurate because of the oversharpening effects.

In addition to accuracy and stability, computational time required in a numerical scheme is of practical importance. The performances of the numerical schemes (error vs computational time), as the grids were refined, are shown in Figs. 3.6 and 3.9 for the case studies for a pulse input and Langmuir isotherm, respectively. Moving horizontally from left to right, the best numerical scheme is the one that is met first, since it requires the least CPU time for a certain level of numerical error. These figures enable us to calculate the additional CPU time required when improved accuracy is sought. We emphasize that all flux limiters were implemented in a consistent fashion with the help of built-in MATLAB functions ensuring comparability. The numerical

error is defined as [64]

$$\|E\| = \left(\frac{1}{N_z} \sum_{j=1}^{N_z} |E_j| \right) \quad (3.51)$$

which is the 1-norm of the normalized local errors calculated by point-by-point comparison with analytical solution and OCFE for case studies A and B, respectively.

3.7.1 Case study A

Elution profiles of case study A are given in Figs. 3.4 and 3.5. The equilibrium theory model results in discontinuities as indicated by the sharp fronts of the analytical solutions. Inspection of the results shows that the elution profiles are stable over the entire range of concentration without any spurious oscillation. Therefore, we conclude that all flux limiters resulted in non-oscillatory solutions. Figs. 3.4 and 3.5 also show that the flux limiters have caused smoothing to various degrees, but the increase in accuracy compared to UDS is obvious for all of them. The analysis of accuracy is more difficult in the case of the Langmuir isotherm, as its self-sharpening effect compensates for the smoothing caused by numerical dispersion. However, it produces the challenging problem of adjacent sharp fronts and smooth regions in the solution as shown in Fig. 3.4(b).

It is also clear from these figures that the superbee flux limiter offers the highest level of accuracy, as indicated by the sharpness of the elution profile in all simulations both under linear and nonlinear conditions. On the other hand, the minmod flux limiter comes last under all conditions, as it causes the maximum amount of smoothing.

Ideally, the elution profiles for linear isotherm must be symmetric, but all flux limiters show a certain degree of artificial asymmetry (Figs. 3.4(a) and 3.5(a)). It can be inferred from the results that the artificial asymmetry has a direct relation with the level of accuracy. For instance, the superbee flux limiter offers the highest accuracy and, at the same time, suffers from the highest asymmetry. However, in this case study, no flux limiter exceeded the reference analytical solutions in sharpness. Therefore, none of them is rejected for oversharpening effects.

Fig. 3.6 shows that van Leer, minmod, and UDS demand comparable computational times, whereas CPU time for the MC, superbee, and Koren flux limiters were significantly higher for a certain level of accuracy or error. Although the CPU time for UDS was relatively low, it could not provide high level of accuracy like van Leer and minmod. Actually, going from left to right, especially at the low error region, we first hit van Leer indicating this to be the flux limiter of choice among others. The smooth functional form of van Leer flux limiter appears to have favorable effects on convergence (and computational time) while others, such as MC, suffer from nonsmooth formulas.

3.7.2 Case study B

Elution profiles of case study B are given in Figs. 3.7 and 3.8. Unlike case study A, sharp fronts were smoothed because of axial dispersion and mass-transfer resistance. Nevertheless, the elution profiles were observed to be stable over the entire range of concentration without any spurious oscillation as in case study A. Therefore, we conclude that all flux limiters resulted in non-oscillatory solutions for this case as well.

(a)

(b)

Figure 3.4: Case study A (equilibrium theory model), elution profiles for a pulse input: (a) linear isotherm; (b) Langmuir isotherm ($N_z = 400$).

(a)

(b)

Figure 3.5: Case study A (equilibrium theory model), elution profiles for a step input: (a) linear isotherm; (b) Langmuir isotherm ($N_z = 400$).

Figure 3.6: Numerical error versus computational time for different flux limiters for case study A, using a pulse input and Langmuir isotherm at time $t = 210$ s. Symbols refer to the number of grid points.

It is also clear from the results that all flux limiters significantly increased the accuracy compared to UDS, but to various degrees indicated by the amount of smoothing they cause. On the other hand, it is evident that except for minmod, all other flux limiters are remarkably comparable to OCFE in sharpness.

Asymmetric effects were also visible, although to a lower extent, in case study B. However, unlike case study A, the undesirable oversharping effects appeared in the elution profiles. It is clear that the superbee flux limiter has exceeded the upper reference solution, namely, OCFE. Therefore, in terms of oversharping, it may not be suitable for the simulation of chromatographic model equations.

The numerical error is plotted versus CPU time in Fig. 3.9 for case study B. Compared to case study A, there was generally an increase in computational time for flux limiters when the axial dispersion and mass-transfer resistance were included.

The best flux limiter is found by moving from left to right in Fig. 3.9 for a certain value of error. Again, we observe that the van Leer flux limiter comes first for a wide range of error values. The computational times of MC, superbee, and Koren flux limiters were significantly higher than those of UDS, minmod, and van Leer for the simulation of detailed model as well.

Based on the simulation results with actual data, presented in the above case studies, the van Leer flux limiter in the domain of finite-volume schemes, shows the most suitability for solving chromatographic model equations in terms of stability, accuracy, and computational time.

3.7.3 Comparison of TVD and WENO schemes

We compared the best candidate from TVD flux limiters, that is van Leer flux limiter with third-order WENO scheme on the problem given in case study B for the Langmuir

(a)

(b)

Figure 3.7: Case study B (detailed model), elution profiles for a pulse input: (a) linear isotherm; (b) Langmuir isotherm ($N_z = 400$).

(a)

(b)

Figure 3.8: Case study B (detailed model), elution profiles for a step input: (a) linear isotherm; (b) Langmuir isotherm ($N_z = 400$).

Figure 3.9: Numerical error versus computational time for different flux limiters for case study B, using a pulse input and Langmuir isotherm at time $t = 210$ s. Symbols refer to the number of grid points.

isotherm and a pulse input. The results are shown in Fig. 3.10. It is obvious that the results are qualitatively very close to each other in terms of accuracy. The run time for van Leer is 7.5 s and for WENO is 8.0 s. These imply that these schemes are highly competitive both in terms of accuracy and CPU time. Although looking at the formulation suggest that WENO is easier to implement than TVD schemes.

3.8 Interim conclusion

Several accurate, fast, and stable numerical schemes for solving chromatographic model equations, especially in the presence of shock fronts, were investigated in this chapter. Existing solution techniques, i.e. finite-difference and finite-element methods, were briefly reviewed and compared with finite-volume method, which so far has been little applied to the solution techniques of model equations in the chromatographic community. One of the well-established, accurate, and stable finite-volume techniques includes the application of appropriate flux limiters. Important flux limiters were implemented on a class of high-resolution central schemes. It was found that the TVD flux limiters can all fulfill stability requirements while maintaining a high level of accuracy in accordance with the TVD properties. Nonetheless, the TVD flux limiters are different in terms of accuracy and computational time, but in general, they are more accurate than UDS. Based on the simulation results with practical data, the van Leer flux limiter in the domain of TVD finite-volume schemes was found to be the most suitable limiter for solving chromatographic model equations. It offers second-order accuracy for smooth regions, and does not exhibit oversharping effects. It is also symmetric by definition. In addition, the computational time of the van Leer flux limiter is close to that of UDS, whereas its accuracy is much higher. It was also found to handle shock fronts efficiently.

We also showed that the third-order WENO scheme can be comparable to the van Leer

Figure 3.10: Comparison of UDS, van Leer flux limiter, and third-order WENO scheme on the detailed model for Langmuir isotherm and a pulse input. The run times for UDS, van Leer, and WENO are 3.3, 7.5, and 8.0 s, accordingly ($N_z = 400$).

flux limiter in terms of speed and accuracy. It also has the advantage if being simpler in implementation.

Although this study was carried out for a single-column, single-component chromatographic adsorption process, the analysis can be extended to a binary separation in a multi-column process (e.g., simulated moving bed). The general conclusions will hold and should be useful for large-scale process optimization using evolutionary algorithms (e.g., genetic algorithm), or for developing optimizing controllers for continuous chromatographic processes. In fact, we have extensively used the proposed WENO scheme for solving model equations arising in Chapters 5 and 6.

Nomenclature

A	column cross-sectional area [m^2]
a	local propagation speed [cm/s]
a_p	external surface area of the solid particles [$1/m$]
c	concentration of species in fluid phase [g/L]
D	column diameter [mm]
$D_{ax,i}$	axial dispersion coefficient of component i [cm^2/s]
$D_{eff,i}$	pore diffusion coefficient of component i [cm^2/s]
E_j	local numerical error [-]
f	convective flux [$\text{g}/(\text{m}^2 \text{ s})$]
F	total flux [$\text{g}/(\text{m}^2 \text{ s})$]
H_i	Henry constant of component i [-]
J	diffusive flux [$\text{g}/(\text{m}^2 \text{ s})$]
K_i	equilibrium constant of component i in Langmuir isotherm [L/g]
$k_{ext,i}$	fluid to particle mass transfer coefficient [m/s]
k_l	lumped mass transfer coefficient [$1/\text{s}$]
L	column length [cm]
N_c	number of components [-]
N_z	number of discretized cells in z direction [-]
n_i	solid phase concentration of component i [g/L]
Q	volumetric flow rate [mL/min]
r_j	dimensionless local gradient [-]
S_G	source term
v	interstitial velocity [cm/s]
V	volume [m^3]
y	generic conserved quantity

Greek letters

Δ	difference operator [-]
ε	overall void fraction of column [-]
ε_e	external void fraction of column [-]
ε_p	internal void fraction of adsorbent particles [-]
ρ	fluid phase density [g/L]
ϕ	flux limiter function [-]
ω	weight factor for the WENO scheme [-]

Subscripts and superscripts

<i>ax</i>	axial dispersion
<i>cont</i>	continuous
<i>F</i>	feed
<i>High</i>	high order
<i>i</i>	component index
<i>in</i>	inlet
<i>inj</i>	injection
<i>j</i>	space discretization index
<i>L</i>	left
<i>Low</i>	low order
<i>n</i>	time discretization index
<i>p</i>	intra-particle
<i>ref</i>	reference
<i>R</i>	right
<i>*</i>	equilibrium

Chapter 4

Analytical Comparison of Single-Column Chromatography and SMB

Despite the high value of products produced by chromatographic separation, minimizing the working capital is an important factor in profitability of a production plant. There is a demand for quick analysis for adopting a new operating point in response to a deliberate modification or under the effect of any disturbance.

Continuous chromatographic separation is the method of choice for large-scale production due to its higher productivity and robustness [4, 29]. Simulated moving bed (SMB), introduced in 1960 [28], has become the benchmark in this regard. Backed by the celebrated triangle theory [72], it is possible to identify the region of complete separation and find a relation between decision variables and performance indicators in relatively a straightforward manner. Ideally, all we need is the adsorption isotherm.

Although single-column chromatography (SCC) does not appear to be highly competitive, it is still attractive due to higher flexibility and lower capital investment [73]. In this chapter, under equilibrium theory assumptions, we analyze SMB and SCC in both linear and nonlinear ranges of operation. For Langmuir isotherm, new analytical results are utilized for obtaining the triangular region of the SMB process [72] and elution profiles of the SCC process [49].

We will show that, at their optimal operating points, there are certain similarities between SMB and SCC when they are compared on a fair basis. Thanks to equilibrium theory, it is possible to highlight optimal operating points and theoretical degrees of freedom for both processes without any need to elaborate on time-consuming numerical methods and multi-objective optimization algorithms. We will also explore the relations between isotherm parameters and performance indicators under equilibrium theory assumptions.

4.1 Problem statement

The schematic diagrams of the SMB and SCC processes are given in Figs. 4.1 and 4.2, respectively. General assumptions are given as follows. We will elaborate on the details and modifications of assumptions in appropriate places:

- A linear/Langmuir isotherm describes the equilibrium.
- A four-section SMB with four identical columns is considered.
- The length of the SCC unit, represented by L , is equal to the overall length of the SMB unit.
- The column cross-sectional area, overall void fraction, and maximum allowable pressure drop are the same for both units.
- Complete separation and complete recovery are sought in both SCC and SMB units.
- Only physical constraints arising from maximum allowable pressure drop on flow rates are considered.

Complete recovery necessitates that we collect only two fractions as products in SCC, and complete separation suggests that the purity values must be 100% in both extract and raffinate streams. In the following, we will investigate the constraints arising from these and other assumptions in order to sort out dependent and independent decision variables in a systematic way. The degrees of freedom are equal to the number of independent decision variables. We will derive the performance indicators and other important parameters in terms of the independent variables.

Under the assumption of complete separation and recovery, productivity can be defined as

$$Pr \equiv \frac{\text{Mass of feed processed per unit time}}{\text{Mass of stationary phase}} \quad (4.1)$$

and desorbent requirement can be defined as

$$Dr \equiv \frac{\text{Overall desorbent flow rate}}{\text{Mass of feed processed per unit time}} \quad (4.2)$$

The overall desorbent flow rate in the definition above includes both desorbent flow rate and feed flow rate as a whole.

The pressure drop in the column is calculated using Darcy's law [73]:

$$\Delta P = \frac{\phi u L \mu}{d_p^2} \quad (4.3)$$

where ϕ is an empirical constant, which is known as the resistance parameter. u is superficial velocity, L is characteristic length (for column or section), d_p is particle diameter, and μ is viscosity. From this point onward, we lump all physical constants into a single parameter $\alpha = \phi\mu/d_p^2$ for brevity.

4.2 Simulated moving bed

4.2.1 Linear isotherm

For SMB, productivity is ideally defined as [4]

$$Pr = \frac{c_T^F Q^F}{(1 - \varepsilon) \rho_s V_T} \quad (4.4)$$

Figure 4.1: An SMB process with four sections and four identical columns (one column per section).

Figure 4.2: A single-column chromatographic (SCC) process for a binary separation with two fractions.

where V_T is the total volume of the SMB unit.

Moreover, the dimensionless flow rates are defined as [4]

$$m_j = \frac{Q^j t^* - \varepsilon V}{(1 - \varepsilon)V} \quad (4.5)$$

V is the volume of each column (i.e., one-quarter of V_T here), t^* is the switching time, and ε is the overall void fraction of column.

By substitution, one can obtain

$$Pr = \frac{c_T^F(m_3 - m_2)}{4\rho_s t^*} \quad (4.6)$$

From triangle theory for a linear isotherm [4], one can infer that maximum productivity and minimum desorbent requirement occur at a point where

$$m_1 = H_2, m_2 = H_1, m_3 = H_2, m_4 = H_1 \quad (4.7)$$

Indexes 1 and 2 refer to less retained and more retained compounds, respectively. Therefore

$$Pr = \frac{c_T^F(H_2 - H_1)}{4\rho_s t^*} \quad (4.8)$$

Furthermore, Eq. 4.5 can be written for Q^j as

$$Q^j = \frac{\varepsilon V}{t^*} \left(1 + \frac{(1 - \varepsilon)}{\varepsilon} m_j \right) \quad (4.9)$$

By summing up all Q^j values, we obtain

$$\Sigma Q^j = \frac{4\varepsilon V}{t^*} \left(1 + \frac{(1 - \varepsilon)}{\varepsilon} \frac{(H_2 + H_1)}{2} \right) \quad (4.10)$$

From Eq. 4.10, we can derive t^*

$$t^* = \frac{4\varepsilon V}{\Sigma Q^j} \left(1 + \frac{(1 - \varepsilon)}{\varepsilon} \frac{(H_2 + H_1)}{2} \right) \quad (4.11)$$

It is obvious that maximum productivity can be obtained at minimum allowable switching time, and —regardless of physical limitations—this occurs when the sum of Q^j values is maximized. However, we have not defined any constraint on Q^j yet.

Regarding Darcy's equation (Eq. 4.3), the pressure drop in each section can be defined as

$$\Delta P_j = \alpha \frac{Q^j L}{A} \quad (4.12)$$

where A is the cross-sectional area of column.

On the other hand, the sum of ΔP_j values must be equal to maximum allowable pressure drop, ΔP_{max} , to obtain maximum value for each Q^j . Therefore

$$\Delta P_{max} = \alpha \frac{\Sigma Q^j L}{A} \quad (4.13)$$

By combining Eqs. 4.11 and 4.13, we obtain

$$t^* = \frac{\alpha L^2}{4\Delta P_{max}} \left(\varepsilon + (1 - \varepsilon) \frac{(H_2 + H_1)}{2} \right) \quad (4.14)$$

Besides, because cycle time is related to switching as $t_{cy} = 4t^*$, we can write

$$t_{cy} = \frac{\alpha L^2}{\Delta P_{max}} \left(\varepsilon + (1 - \varepsilon) \frac{(H_2 + H_1)}{2} \right) \quad (4.15)$$

Knowing that

$$Q^F = \frac{(1 - \varepsilon)V}{t^*} (m_3 - m_2) \quad (4.16)$$

A similar relation can be found between feed flow rate and pressure drop

$$Q^F = A \frac{\Delta P_{max}}{\alpha L} \frac{(1 - \varepsilon)(H_2 - H_1)}{\left(\varepsilon + (1 - \varepsilon) \frac{(H_2 + H_1)}{2} \right)} \quad (4.17)$$

Eq. 4.14 can be finally substituted in Eq. 4.8 to obtain productivity

$$Pr = \frac{c_T^F}{\rho_s} \frac{\Delta P_{max}}{\alpha L^2} \frac{(H_2 - H_1)}{\left(\varepsilon + (1 - \varepsilon) \frac{(H_2 + H_1)}{2} \right)} \quad (4.18)$$

Furthermore, desorbent requirement is defined as [4]

$$Dr = \frac{Q^F + Q^D}{c_T^F Q^F} \quad (4.19)$$

Eq. 4.19 can be rewritten in terms of dimensionless flow rates as

$$Dr = \frac{1}{c_T^F} \left(1 + \frac{m_1 - m_4}{m_3 - m_2} \right) \quad (4.20)$$

m_j s can be substituted by respective values from Eq. 4.7

$$Dr = \frac{1}{c_T^F} \left(1 + \frac{H_2 - H_1}{H_2 - H_1} \right) \quad (4.21)$$

Hence, after simplifying, we obtain

$$Dr = \frac{2}{c_T^F} \quad (4.22)$$

4.2.2 Langmuir isotherm

The values of dimensionless flow rates at the optimal operating point for Langmuir isotherm are given by Mazzotti [72] as follows

$$m_1 = H_2 \quad (4.23)$$

$$m_2 = \frac{\omega_2^F H_1}{H_2} \quad (4.24)$$

$$m_3 = \frac{\omega_2^F (H_1 (H_1 - \omega_1^F) + \omega_1^F (H_2 - H_1))}{H_1 (H_2 - \omega_1^F)} \quad (4.25)$$

$$m_4 = \frac{1}{2} \left\{ m_3 + H_1 + K_1 c_1^F (m_3 - m_2) - \sqrt{[m_3 + H_1 + K_1 c_1^F (m_3 - m_2)]^2 - 4m_3 H_1} \right\} \quad (4.26)$$

where ω_i^F is the characteristic parameter calculated at feed concentration [72].

Eq. 4.9 can be used in the case of Langmuir isotherm as well to obtain an expression for switching time, though in order to keep the equation short, the term Σm_j will not be replaced by the respective m_j values

$$t^* = \frac{4\varepsilon V}{\Sigma Q^j} \left(1 + \frac{(1 - \varepsilon) \Sigma m_j}{\varepsilon} \frac{1}{4} \right) \quad (4.27)$$

ΣQ^j can be eliminated from Eq. 4.27 with the help of Eq. 4.13 and switching time can be replaced by cycle time

$$t_{cy} = \frac{\alpha L^2}{\Delta P_{max}} \left(\varepsilon + (1 - \varepsilon) \frac{\Sigma m_j}{4} \right) \quad (4.28)$$

Having Eq. 4.16 at hand, feed flow rate can be related to the maximum allowable pressure drop and isotherm parameters in a similar fashion

$$Q^F = A \frac{\Delta P_{max}}{\alpha L} \frac{(1 - \varepsilon) \frac{\omega_1^F \omega_2^F (H_2 - H_1)^2}{H_1 H_2 (H_2 - \omega_1^F)}}{\left(\varepsilon + (1 - \varepsilon) \frac{\Sigma m_j}{4} \right)} \quad (4.29)$$

Same steps as of linear isotherm can be taken to obtain productivity and desorbent requirement. Therefore, productivity becomes

$$Pr = \frac{c_T^F}{\rho_s} \frac{\Delta P_{max}}{\alpha L^2} \frac{\frac{\omega_1^F \omega_2^F (H_2 - H_1)^2}{H_1 H_2 (H_2 - \omega_1^F)}}{\left(\varepsilon + (1 - \varepsilon) \frac{\Sigma m_j}{4} \right)} \quad (4.30)$$

and desorbent requirement becomes

$$Dr = \frac{1 + \frac{H_1 H_2 (H_2 - \omega_1^F) (H_2 - m_4)}{\omega_1^F \omega_2^F (H_2 - H_1)^2}}{c_T^F} \quad (4.31)$$

4.3 Single-column chromatography

4.3.1 Linear isotherm

Similar to SMB, here we start from productivity to obtain equivalent expressions for SCC. Assuming complete separation and complete recovery, for single-column chromatography, productivity is ideally defined as

$$Pr = \frac{c_T^F V_{inj}}{(1 - \varepsilon) \rho_s V_T t_{cy}} \quad (4.32)$$

Figure 4.3: Touching-band eluted peaks of the SCC process under linear isotherm.

Figure 4.4: Touching-band eluted peaks of the SCC process under Langmuir isotherm.

As depicted in Fig. 4.3, maximum productivity at complete separation and recovery must be sought at touching-band condition or in other words incipient baseline separation, where there is no overlapping and no gap between eluted peaks. In such conditions, we have

$$t_{cy} = 2t_p = \frac{2V_{inj}}{Q^D} \quad (4.33)$$

where t_p is the pulse width. This can be directly substituted in Eq. 4.32

$$Pr = \frac{c_T^F Q^D}{2(1 - \varepsilon)\rho_s V_T} \quad (4.34)$$

In order to maximize productivity, Q^D must be maximized, and as described for the case of SMB, maximum allowable pressure drop along the column limits Q^D

$$\Delta P_{max} = \alpha \frac{Q^D}{A} L \quad (4.35)$$

Combining Eqs. 4.34 and 4.35 gives

$$Pr = \frac{c_T^F}{\rho_s} \frac{\Delta P_{max}}{\alpha L^2} \frac{1}{2(1 - \varepsilon)} \quad (4.36)$$

Under the linear condition, the retention time of component i is defined as

$$t_{R,i} = \frac{\varepsilon V_T}{Q^D} \left(1 + \frac{(1 - \varepsilon)}{\varepsilon} H_i \right) \quad (4.37)$$

Under the assumptions of complete separation and complete recovery, the value of cycle time must be equal to twice the difference between retention times of components 2 and 1

$$t_{cy} = 2(t_{R,2} - t_{R,1}) \quad (4.38)$$

Therefore

$$t_{cy} = \frac{2(1 - \varepsilon)V_T}{Q^D}(H_2 - H_1) \quad (4.39)$$

With the help of Eq. 4.35, Q^D can be eliminated from Eq. 4.39 to obtain a direct relation between cycle time and pressure drop

$$t_{cy} = \frac{\alpha L^2}{\Delta P_{max}} [2(1 - \varepsilon)(H_2 - H_1)] \quad (4.40)$$

Knowing that $t_p = V_{inj}/Q^D$, injection volume can also be represented by a useful equation

$$\frac{V_{inj}}{V_T} = (1 - \varepsilon)(H_2 - H_1) \quad (4.41)$$

For the sake of comparison with SMB, an average feed flow rate can be defined for single-column chromatography as

$$Q^F = \frac{V_{inj}}{t_{cy}} \quad (4.42)$$

By substituting for t_{cy} from Eq. 4.40 and for V_{inj} from Eq. 4.41, Eq. 4.42 can be written as a function of pressure drop

$$Q^F = A \frac{\Delta P_{max}}{\alpha L} \frac{1}{2} \quad (4.43)$$

Similar to the case of SMB, desorbent requirement can be defined as

$$Dr = \frac{Q^D t_{cy} + V_{inj}}{V_{inj} c_T^F} \quad (4.44)$$

Substituting for t_{cy} from Eq. 4.33 gives

$$Dr = \frac{Q^D \frac{2V_{inj}}{Q^D} + V_{inj}}{V_{inj} c_T^F} \quad (4.45)$$

Finally

$$Dr = \frac{3}{c_T^F} \quad (4.46)$$

4.3.2 Langmuir isotherm

Similar approach can be taken to obtain explicit values for the productivity and desorbent requirement of SCC under Langmuir isotherm. Here again, maximum productivity at complete separation and recovery must be sought at touching-band condition,

where there is no overlapping and no gap between eluted peaks. In such conditions, we have incipient baseline separation between peaks, which imposes an additional constraint on the problem. Here we need explicit relations for the retention times of two components. We also need a criterion on incipient baseline separation. Rajendran and Mazzotti [49] have given useful expressions for analytical solutions for a chromatographic cycle. A typical chromatogram is shown in Fig. 4.4. With reference to this figure, cycle time can be expressed as

$$t_{cy} = t_{R,20} - t_{R,1} \quad (4.47)$$

where $t_{R,1}$ is the retention time of the less retained compound and $t_{R,20}$ is the point where the tail of more retained compound ends. We make this assumption here that the concentration plateau on less retained compound still exists as shown in Fig. 4.4, which means there is no wave interaction between the shock front and the continuous part of the elution profile of the less retained compound [49]. Therefore, $t_{R,1}$ can be readily obtained from the following formula for the shock path with $x = 1$ (see Table 6 in Rajendran and Mazzotti [49])

$$t_{R,1} = \frac{L}{v} \left(1 + \frac{1-\varepsilon}{\varepsilon} \omega_1^F \right) \quad (4.48)$$

where v is the interstitial velocity and ω_1^F is the characteristic parameter for component 1 at feed concentration. Similarly

$$t_{R,20} = \frac{L}{v} \left(1 + \frac{1-\varepsilon}{\varepsilon} H_2 \right) + t_p \quad (4.49)$$

where $t_p = V_{inj}/Q^D$ is the pulse width. Therefore, Eq. 4.47 can be written as

$$t_{cy} = \frac{\varepsilon V_T}{Q^D} \left(\frac{1-\varepsilon}{\varepsilon} (H_2 - \omega_1^F) \right) + \frac{V_{inj}}{Q^D} \quad (4.50)$$

On the other hand, because of the incipient baseline separation condition, the following equation must hold (see Table 6 in Rajendran and Mazzotti [49])

$$\frac{v}{L} \frac{\varepsilon}{1-\varepsilon} \frac{H_1 H_2}{\omega_1^F \omega_2^F} \frac{(H_2 - \omega_1^F) t_p}{(H_2 - H_1)^2} = 1 \quad (4.51)$$

Replacing t_p and v with proper terms and rearrangement gives

$$\frac{V_{inj}}{V_T} = (1-\varepsilon) \frac{\omega_1^F \omega_2^F}{H_1 H_2} \frac{(H_2 - H_1)^2}{H_2 - \omega_1^F} \quad (4.52)$$

Therefore, cycle time can be written as

$$t_{cy} = \frac{(1-\varepsilon) V_T}{Q^D} \left((H_2 - \omega_1^F) + \frac{\omega_1^F \omega_2^F}{H_1 H_2} \frac{(H_2 - H_1)^2}{H_2 - \omega_1^F} \right) \quad (4.53)$$

After eliminating V_T and Q^D

$$t_{cy} = \frac{\alpha L^2}{\Delta P_{max}} (1-\varepsilon) \left((H_2 - \omega_1^F) + \frac{\omega_1^F \omega_2^F}{H_1 H_2} \frac{(H_2 - H_1)^2}{H_2 - \omega_1^F} \right) \quad (4.54)$$

The expressions, namely Eqs. 4.35, 4.52, and 4.54 can be used here to obtain a relation for average feed flow rate when Langmuir isotherm prevails

$$Q^F = A \frac{\Delta P_{max}}{\alpha L} \frac{1}{1 + \frac{H_1 H_2}{\omega_1^F \omega_2^F} \left(\frac{H_2 - \omega_1^F}{H_2 - H_1} \right)^2} \quad (4.55)$$

Eqs. 4.52 and 4.54 can be readily used within Eq. 4.32 to obtain productivity

$$Pr = \frac{c_T^F}{\rho_s} \frac{\Delta P_{max}}{\alpha L^2} \frac{1}{(1 - \varepsilon) \left[1 + \frac{H_1 H_2}{\omega_1^F \omega_2^F} \left(\frac{H_2 - \omega_1^F}{H_2 - H_1} \right)^2 \right]} \quad (4.56)$$

For desorbent requirement, we need to replace the expressions we obtained earlier for injection volume and cycle time into Eq. 4.44 accordingly

$$Dr = \frac{V_{inj} + V_{inj} + (1 - \varepsilon)V_T(H_2 - \omega_1^F)}{V_{inj} c_T^F} \quad (4.57)$$

Finally

$$Dr = \frac{2 + \frac{H_1 H_2}{\omega_1^F \omega_2^F} \left(\frac{H_2 - \omega_1^F}{H_2 - H_1} \right)^2}{c_T^F} \quad (4.58)$$

The relations for productivity, desorbent requirement, feed flow rate, and cycle time for SCC and SMB under linear and Langmuir isotherms are summarized in Tables 4.1 and 4.2, respectively.

Table 4.1: Summary of important equations obtained for SCC and SMB subject to linear isotherm.

Parameter	SCC	Eq.	SMB	Eq.
Pr	$\frac{c_T^F}{\rho_s} \frac{\Delta P_{max}}{\alpha L^2} \frac{1}{2(1-\varepsilon)}$	4.36	$\frac{c_T^F}{\rho_s} \frac{\Delta P_{max}}{\alpha L^2} \frac{(H_2 - H_1)}{\left(\varepsilon + (1-\varepsilon) \frac{(H_2 + H_1)}{2} \right)}$	4.18
Dr	$\frac{3}{c_T^F}$	4.46	$\frac{2}{c_T^F}$	4.22
Q^F	$A \frac{\Delta P_{max}}{\alpha L} \frac{1}{2}$	4.43	$A \frac{\Delta P_{max}}{\alpha L} \frac{(1-\varepsilon)(H_2 - H_1)}{\left(\varepsilon + (1-\varepsilon) \frac{(H_2 + H_1)}{2} \right)}$	4.17
t_{cy}	$\frac{\alpha L^2}{\Delta P_{max}} [2(1 - \varepsilon)(H_2 - H_1)]$	4.40	$\frac{\alpha L^2}{\Delta P_{max}} \left(\varepsilon + (1 - \varepsilon) \frac{(H_2 + H_1)}{2} \right)$	4.15

Table 4.2: Summary of important equations obtained for SCC and SMB subject to Langmuir isotherm.

Parameter	SCC	Eq.	SMB	Eq.
P_r	$\frac{c_T^F}{\rho_s} \frac{\Delta P_{max}}{\alpha L^2} \frac{1}{(1-\varepsilon) \left[1 + \frac{H_1 H_2}{\omega_1^F \omega_2^F} \left(\frac{H_2 - \omega_1^F}{H_2 - H_1} \right)^2 \right]}$	4.56	$\frac{c_T^F}{\rho_s} \frac{\Delta P_{max}}{\alpha L^2} \frac{\omega_1^F \omega_2^F}{H_1 H_2} \frac{(H_2 - H_1)^2}{H_2 - \omega_1^F} \frac{1}{\left(\varepsilon + (1-\varepsilon) \frac{\sum m_i}{4} \right)}$	4.30
Dr	$2 + \frac{H_1 H_2}{\omega_1^F \omega_2^F} \left(\frac{H_2 - \omega_1^F}{H_2 - H_1} \right)^2 \frac{1}{c_T^F}$	4.58	$1 + \frac{H_1 H_2}{\omega_1^F \omega_2^F} \frac{(H_2 - \omega_1^F)(H_2 - m_4)}{(H_2 - H_1)^2} \frac{1}{c_T^F}$	4.31
Q^F	$A \frac{\Delta P_{max}}{\alpha L} \frac{1}{1 + \frac{H_1 H_2}{\omega_1^F \omega_2^F} \left(\frac{H_2 - \omega_1^F}{H_2 - H_1} \right)^2}$	4.55	$(1-\varepsilon) \frac{\omega_1^F \omega_2^F}{H_1 H_2} \frac{(H_2 - H_1)^2}{H_2 - \omega_1^F} \frac{1}{\left(\varepsilon + (1-\varepsilon) \frac{\sum m_i}{4} \right)}$	4.29
t_{cy}	$\frac{\alpha L^2}{\Delta P_{max}} (1-\varepsilon) \left((H_2 - \omega_1^F) + \frac{\omega_1^F \omega_2^F}{H_1 H_2} \frac{(H_2 - H_1)^2}{H_2 - \omega_1^F} \right)$	4.54	$\frac{\alpha L^2}{\Delta P_{max}} \left(\varepsilon + (1-\varepsilon) \frac{\sum m_i}{4} \right)$	4.28

4.4 Results and discussion

With regard to the equations summarized in Tables 4.1 and 4.2, the first outcome of this analysis is that at optimal points, there are one-to-one similarities between SCC and SMB in terms of corresponding parameters, namely productivity, desorbent requirement, feed flow rate, and cycle time. The similarities are not limited to linear isotherm and are clearly extended to the case of Langmuir isotherm. Furthermore, it is worthy of attention that the equations obtained for Langmuir isotherm can be simplified to the case of linear isotherm either at very low feed concentrations or where Langmuir equilibrium constants are set to zero ($K_i = 0$). Equivalently, we can set $\omega_1^F = H_1$ and $\omega_2^F = H_2$.

It is also important to note that meaningful groups of parameters are identified in the results and they have their counterparts for SCC and SMB as given in Tables 4.1 and 4.2. Looking at productivity for example, the first group carries the effect of feed concentration. The second group carries the effect of pressure drop and geometry, and the third one carries the effect of isotherm parameters.

Although we relied on equilibrium theory as the ideal framework, we believe that the results can also be used for 'order of magnitude' analysis for the effects of decision variables even for non-ideal problems. This may serve as a useful tool for practitioners who need to make quick estimation of the effects of change in operating conditions.

In this work, we investigate the effect of change in feed concentration and Henry constants on the important parameters with the help of numerical case studies. We have considered two case studies for guaifenesin (case A) and Tröger's base (case B) whose isotherm parameters are given in Table 4.3. The same Henry constants are used for linear isotherms. The physical properties are kept constant for two case studies as given in Table 4.4. It must be noted that for the case of changing Henry constants, the same K_i values from the numerical case studies are used for this analysis.

Table 4.3: Isotherm parameters used in the case studies. Note that for the linear isotherms, K_i values are simply set to zero.

Parameter	Case A (guaifenesin) [67]	Case B (Tröger's base) [74]	Unit
H_1	1.41	2.18	-
H_2	3.49	6.45	-
K_1	0.0135	0.065	L/g
K_2	0.0550	0.39	L/g

Table 4.4: Physical parameters.

Parameter	Value	Unit
D	1	cm
L	10	cm
ε	0.704	-
α	7.59×10^8	Pa.s/m ²
ρ_s	2027.03	g/L

4.4.1 Effects of feed concentration

Results given in Tables 4.1 and 4.2 suggest that for fixed geometry and physical properties, the only degree of freedom is the feed concentration for both SCC and SMB at optimal points. Feed concentration has a positive effect on productivity for both SCC and SMB under linear or Langmuir isotherm. For linear isotherm, the effect is merely linear. For Langmuir isotherm however, productivity is a complex, but still increasing function of feed concentration as can be seen in Figs. 4.5(a) and 4.6(a). Nevertheless, the rate of change in productivity for Langmuir isotherm is less than that of linear isotherm.

It is worthy of attention that for case A, the productivity of SCC is higher than that of SMB for the entire range of concentration, but for case B, this order is reversed. This finding suggests that theoretically, SCC can be better than SMB in terms of productivity for certain isotherms.

Comparing Eqs. 4.22 and 4.46, it is clear that single-column chromatography demands more desorbent requirement than SMB for linear range of operation. For Langmuir isotherm, the same argument holds for the case studies considered here as can be seen in Figs. 4.5(b) and 4.6(b), though drawing a general conclusion for Langmuir isotherm is not straightforward. Moreover, desorbent requirement appears as a sole function of feed concentration for linear isotherm, but it is affected by isotherm parameters for Langmuir isotherm.

In contrast to the common practice that cycle time is considered an independent decision variable, for a fixed set of physical properties and geometry, it is a constant for linear isotherm and a sole function of feed concentration for Langmuir isotherm.

Figure 4.5: Performance indicators vs. feed concentration for guaifenesin (case A): (a) productivity; (b) desorbent requirement.

4.4.2 Effects of pressure drop and overall length

The effect of maximum allowable pressure drop is the same for all cases; productivity linearly increases with increasing this parameter. On the other hand, productivity is always inversely related to the square of the overall length of unit. Therefore, ideally, shorter columns are favored to increase productivity. Besides, the fact that productivity appears as a function of the length of unit necessitates that a fair comparison

Figure 4.6: Performance indicators vs. feed concentration for Tröger's base (case B): (a) productivity; (b) desorbent requirement.

between SCC and SMB must be made at a fixed overall length. Conversely, column cross-sectional area has no effect on productivity. On the other hand, desorbent requirement is not affected by any of these parameters.

Feed flow rate has similar functionality when it is compared to productivity. The major difference is that the cross-sectional area of unit directly affects feed flow rate. Therefore, feed flow rate not only is related to the geometry of process through length, it is also a function of cross-sectional area, which means feed flow rate for the two processes must be compared at a fixed A/L ratio. Besides, these results affirm that shorter columns are ideally favored for more feed throughput.

It must be emphasized that optimal cycle time varies with the square of the length of unit. This means, in practical applications, minimum possible switching time might become the active constraint when the length of unit is reduced to increase productivity. The lower limit may be dictated by the response time of switching valves, communication devices, etc.

4.4.3 Effects of Henry constants

With reference to Tables 4.1 and 4.2, Henry constants have a complex effect on the productivity of SMB, but rather simpler effect on the productivity of SCC. In fact, they have no effect on the productivity of SCC in linear range of operation. This can result in a higher productivity for SCC compared to SMB if for example, highly retentive or low-selectivity materials are processed.

As inferred from Figs. 4.7 and 4.8, productivity increases as the difference between two Henry constants increases. It is worthy of attention that for some small regions, where the difference between Henry constants is small, there are chances that theoretically, the productivity of SCC becomes greater than that of SMB.

In linear range of operation, desorbent requirement is solely a function of feed concentration as mentioned earlier. For Langmuir isotherm, it is also a function of isotherm parameters, but not any other parameter. This contrasts the common belief that desorbent requirement must be a function of desorbent flow rate. Moreover, the results reveal that in contrast to productivity, desorbent requirement is completely indepen-

dent of the process scale.

Regarding desorbent requirement, the difference between SCC and SMB is small for small Henry constants, but it approaches a certain limit when H_2 increases as can be seen in Fig. 4.9. Moreover, SMB always has a smaller desorbent requirement compared to SCC.

For SCC, cycle time is related to difference between Henry constants, but for SMB, it is a function of the sum of Henry constants. For a Langmuir isotherm, a similar but more complex functionality is observed. This finding shows that two different phenomena decide on the optimal cycle time values for SCC and SMB.

Figure 4.7: Productivity vs. Henry constants for linear isotherm. Numbers next to the lines are H_1 values. c_T^F is 24 g/L. (Results are the same for the two case studies).

On the other hand, for SCC, similar to cycle time, injection volume is no longer an independent decision variable (see Eqs. 4.41 and 4.52). For linear isotherm, it is just a function of the length of unit, physical properties, and Henry constants. For Langmuir isotherm however, the effect of feed concentration is added and therefore, injection volume also becomes a function of feed concentration.

4.5 Interim conclusion

In this chapter, recent analytical methods were applied to investigate the behavior of single-column chromatography and simulated moving bed at their optimal operating points for the case of complete separation and recovery. It was shown that performance indicators namely, productivity and desorbent requirement can be expressed in similar terms for these processes under equilibrium theory assumptions.

It was identified that feed concentration is the only degree of freedom when geometry and physical properties are kept constant. Hence, all other parameters, such as cycle time, feed flow rate, and injection volume can be expressed as a function of feed concentration in such conditions. In addition, feed concentration has positive effect on both performance indicators (i.e., it increases productivity and decreases desorbent requirement) in the case studies investigated in this work and therefore, the optimal operating point must occur at the maximum possible feed concentration.

(a)

(b)

Figure 4.8: Productivity vs. Henry constants for Langmuir isotherm: (a) guaifenesin (case A); (b) Tröger's base (case B). Numbers next to the lines are H_1 values. c_T^F is 24 g/L.

(a)

(b)

Figure 4.9: Desorbent requirement vs. Henry constants for Langmuir isotherm: (a) guaifenesin (case A); (b) Tröger's base (case B). Numbers next to the lines are H_1 values. c_T^F is 24 g/L.

It was also identified that in some ranges of Henry constants, single-column chromatography can take over simulated moving bed in terms of productivity, but it is always inferior in terms of desorbent requirement.

Based on these results, productivity is theoretically proportional to the inverse of the square of column length. Therefore, shorter columns are favored for increasing productivity. Of course, this means switching time must be smaller accordingly though it might be constrained by hardware limitations, and so is productivity. In practice, band broadening effects can also pose a minimum value on the length of the unit [75, 76]. In summary, it may not be possible to freely reduce the length in practice as suggested by these theoretical studies, though further investigation in areas such as capillary chromatography looks attractive.

In the framework of complete separation and recovery, extension of the results of single-column chromatography to a multi-component case would be straightforward because we can simply divide the elution profile into any number of pure fractions similar to a binary separation. However, for SMB, more effluents in addition to extract and raffinate must be added or we need to cascade multiple units, which would make the formulation and operation more difficult.

Nomenclature

A	column cross sectional area [m^2]
c_T^F	total feed concentration [g/L]
Dr	desorbent requirement [L/g]
d_P	particles diameter [μm]
H_i	Henry constant of component i [-]
K_i	equilibrium constant of component i in Langmuir isotherm [L/g]
L	overall length [cm]
m_j	dimensionless flow-rate ratio [-]
Pr	productivity [g/(min g)]
ΔP	pressure drop [bar]
Q	volumetric flow rate [mL/min]
t^*	switching time [s]
t_{cy}	cycle time [s]
$t_{R,i}$	retention time of component i [s]
u	superficial velocity [cm/s]
V	volume of one column (SMB) [m^3]
V_{inj}	injection volume [μL]
V_T	overall volume [m^3]
v	interstitial velocity [cm/s]
z	axial coordinate [m]

Greek letters

α	lumped physical parameter defined as $\alpha = \phi\mu/d_p^2$ [Pa.s/ m^2]
ε	overall void fraction of column [-]
ϕ	resistance parameter [-]
ω	characteristic parameter [-]
μ	viscosity [Pa.s]
ρ	density [g/L]

Subscripts and superscripts

ax	axial
D	desorbent
F	feed
i	component index
in	inlet
j	section
s	solid/stationary phase

Chapter 5

Multi-Objective Optimization of the ISCC Process

In this chapter, optimization of the ISCC process is formulated with two objectives: maximizing productivity and minimizing desorbent requirement. There exists a trade-off between these performance indicators as they may not be simultaneously maximized/minimized at a single operating point. Therefore, optimal solutions appear as a set of points, which are non-dominated with respect to one another. Meanwhile, the constraints arising from hardware limitations such as maximum allowable pressure drop and product specifications such as minimum purity must be accounted properly. A popular way of incorporating the nonlinear constraints is augmenting objectives with penalty functions, which is how we formulated the optimization problem. See Section 5.2.1 for further details.

In this work, we have used NSGA-II (non-dominated sorting genetic algorithms) [77] to search for optimal points. NSGA-II is an evolutionary algorithm (EA), which mimics natural evolution to constitute optimization procedures. EAs are different from classical search and optimization procedures in a variety of ways. They excel over calculus-based methods in the sense of escaping from a local optimum [78]. Thus, they are ideal candidates for solving nonlinear, large-scale optimization problems with multiple local optima. They can also be extended to multi-objective optimization in a straight-forward manner [75, 79, 80, 81]. However, EAs are computationally expensive. They also suffer from inability to pinpoint the final solution upon convergence to an optimal point.

5.1 Modeling and process description

Simulation of the improved single-column chromatographic process has been carried out using a detailed one-dimensional model, which considers the convection and axial dispersion in the fluid phase. Linear driving force model is used for approximating the mass transfer dynamics. Material balance and mass transfer rate are expressed by Eqs. 3.3 and 3.7 given in Chapter 3.

The axial dispersion coefficient D_{ax} is calculated using the following correlation [82].

$$\varepsilon Pe = 0.2 + 0.011 Re^{0.48} \quad (5.1)$$

$$Pe = \frac{vd_p}{D_{ax}} \quad (5.2)$$

The pressure drop in the column is calculated using Darcy’s law as given by Eq. 4.3 in Chapter 4.

5.1.1 Separation model

Guaifenesin has been taken as the model chiral compound to separate, where (S)-(+)-guaifenesin is the more retained enantiomer denoted by A and (R)-(–)-guaifenesin is the less retained enantiomer denoted by B throughout this chapter. In optimization, the upper limit of feed concentration has been taken as 35 g/L. Experimentally, we checked the solubility of guaifenesin in heptane-ethanol (65:35,v/v) mixture at room temperature (23°C) to justify the upper limit of feed concentration. This value is in close proximity of the value used by Francotte et al. [67].

5.1.2 Isotherm

The competitive binary Langmuir isotherm of guaifenesin enantiomers in heptane-ethanol (65:35, v/v) mobile phase and on Chiralcel OD stationary phase was taken from literature [67]. The values of process parameters are reported in Table 5.1.

Table 5.1: Physical parameters.

Parameter	Value	Unit	Reference
D	1	cm	-
L	10	cm	-
ε	0.704	-	[67]
H_A	3.49	-	[67]
H_B	1.41	-	[67]
K_A	0.0550	L/g	[67]
K_B	0.0135	L/g	[67]
d_p	20	μm	-
k_l	18.3	1/s	[68]
ϕ	500	-	[73]
μ	6.08×10^{-4}	Pa.s	-
m_{ad}	4.7	g	-

5.1.3 Process description

The details of the process description can be found in Chapter 2. As mentioned earlier, feed, as a train of pulses, is injected by the arrangement of an HPLC pump and an 8 port, 2 position switching valve. This approach is very similar to the conventional stacked injection [24]. However, the elution profile might be continued to the next cycle as there is no limitation for baseline separation in this separation scheme. In addition, partial loop filling allows variable injection volumes, which is necessary for optimization studies.

The maximum desorbent flow rate is dictated by the maximum allowable pressure that the stationary phase Chiralcel OD can withstand (approximately 40-50 bar) or the maximum flow rate that a pump can deliver, whichever comes first.

5.2 Optimization

5.2.1 Problem statement

Optimization of the ISCC process has been formulated as a multi-objective optimization problem to maximize productivity (Pr) and minimize desorbent requirement (Dr), while fulfilling process and product constraints.

The solution domain is defined by decision variables, namely operating parameters to be changed in order to optimize the process. They are injection volume (V_{inj}), cycle time (t_{cy}), desorbent flow rate (Q^D), total feed concentration (c_T^F), and three cut intervals (dt_{c1} , dt_{c2} , and dt_{c3}).

Productivity is defined as

$$Pr = \frac{\int_0^{t_{cy}} (c_A^E + c_B^E) Q^E dt + \int_0^{t_{cy}} (c_A^R + c_B^R) Q^R dt}{m_{ad} t_{cy}} \quad (5.3)$$

where m_{ad} is the mass of adsorbent in the column.

Desorbent requirement is defined as

$$Dr = \frac{t_{cy} Q^D + V_{inj}}{c_T^F V_{inj}} \quad (5.4)$$

The flow rate of raffinate stream is defined as

$$Q^R = \begin{cases} Q^D & \text{if } 0 \leq t - t_{sc} < dt_{c1} \\ 0 & \text{else} \end{cases} \quad (5.5)$$

Similarly, the flow rate of extract stream is defined as

$$Q^E = \begin{cases} Q^D & \text{if } 0 \leq t - t_{sc} - (dt_{c1} + dt_{c2}) < dt_{c3} \\ 0 & \text{else} \end{cases} \quad (5.6)$$

Purities are defined as

$$P_B = \frac{\int_0^{t_{cy}} c_B^R Q^R dt}{\int_0^{t_{cy}} (c_A^R + c_B^R) Q^R dt} \quad (5.7)$$

$$P_A = \frac{\int_0^{t_{cy}} c_A^E Q^E dt}{\int_0^{t_{cy}} (c_A^E + c_B^E) Q^E dt} \quad (5.8)$$

and recoveries are defined as

$$Y_B = \frac{\int_0^{t_{cy}} c_B^R Q^R dt}{c_B^F V_{inj}} \quad (5.9)$$

$$Y_A = \frac{\int_0^{t_{cy}} c_A^E Q^E dt}{c_A^F V_{inj}} \quad (5.10)$$

Constraints dictated by product specifications are purity and recovery and those dictated by hardware limitations are maximum allowable pressure drop across the column and maximum pump flow rate

$$P_i \geq P_i^{min} \quad (i = A, B) \quad (5.11)$$

$$Y_i \geq Y_i^{min} \quad (i = A, B) \quad (5.12)$$

$$\Delta P \leq \Delta P_{max} \quad (5.13)$$

$$Q^D \leq Q_{max}^D \quad (5.14)$$

The range of values for decision variables are given in Table 5.2. They were obtained from the analysis of physical limitations such as solubility limit, valve response time, etc. The maximum allowable pressure drop is taken as 40 bar.

There are also a few logical constraints bounding the decision variables: injection time (V_{inj}/Q^D) cannot be greater than cycle time t_{cy} . Therefore

$$\frac{V_{inj}}{Q^D} < t_{cy} \quad (5.15)$$

and the sum of three assigned cut intervals must be smaller than cycle time t_{cy}

$$\sum_{i=1}^3 dt_{ci} < t_{cy} \quad (5.16)$$

The performance indicators are considered as Dr and $1/Pr$ to suit a minimization problem. The nonlinear inequality constraints on product purity and recovery (Eqs. 5.11 and 5.12) are incorporated in the objective functions as penalty functions

$$J_1 = \frac{1}{(\alpha + Pr)} + \lambda_{pt} f_{pt} \quad (5.17)$$

$$J_2 = Dr + \lambda_{pt} f_{pt} \quad (5.18)$$

where f_{pt} is defined as

$$f_{pt} = \sum_{i=1}^2 \max \left(0, \frac{(P_i^{min} - P_i)}{P_i^{min}} \right) + \sum_{i=1}^2 \max \left(0, \frac{(Y_i^{min} - Y_i)}{Y_i^{min}} \right) \quad (i = A, B) \quad (5.19)$$

α is a very small positive number added to avoid division by zero and λ_{pt} is a penalty factor, regulating the relative weight of the penalty function.

Table 5.2: Range of decision variables.

Decision variable	Range
V_{inj}	300-5000 μL
t_{cy}	10-90 s
Q^D	5-70 mL/min
c_T^F	10-35 g/L
dt_{c1}	1-90 s
dt_{c2}	0.2-90 s
dt_{c3}	1-90 s

5.3 Solution techniques

5.3.1 Multi-objective genetic algorithm

Genetic algorithm (GA) is a nature-inspired stochastic global search method, which was first introduced by Holland [83]. GA is different from classical deterministic search and optimization methods; it has better chance of finding global optima and less possibility to trap in local optima. In fact, it can find multiple optima as well because GA is a multi-point search method. GA begins with generating random points around a given initial guess and terminates when no significant change occurs in the solution. GA uses only objective function values, not derivatives, in the search procedure and this is a major difference it has with gradient-based methods.

In GA terminology, the solution vector of each decision variable is called an individual or a chromosome. Discrete units of these chromosomes, also known as genes, control the characteristics of each individual. For our case, each individual comprises a set of decision variables that is, injection volume, cycle time, desorbent flow rate, feed concentration, and three cut intervals. Collection of individuals is termed as a population.

GA evolves the population in every generation (iteration). In this process only the fittest individuals (parents or children) survive and gradually dominate the entire population. In addition, GA takes into account the feasibility of every individual with respect to problem constraints.

After evaluation of each individual, using objective function values, a relative merit named 'fitness' is assigned to it. The ultimate objective is to maximize the fitness of that population by evolution over generations under specified selection rules [77].

Most multi-objective optimization algorithms use the concept of domination [84]. A solution x_1 is said to dominate the other solution x_2 , if x_1 is no worse than x_2 in all objectives and x_1 is strictly better than x_2 in at least one objective function. This non-dominated set of entire search space is called Pareto-optimal set or simply Pareto set. The corresponding objective function values for a given Pareto-optimal set is called Pareto front. Any effort to improve Pareto solution with respect to any objective will lead to deterioration of at least another objective.

We have chosen NSGA-II (non-dominated sorting genetic algorithm) [77] in MATLAB for optimization programming, which is one of the most powerful and robust multi-objective optimization algorithms. In this algorithm, solutions are categorized based on sorting their ranks into layers spearheaded by Pareto front. This means the fittest

individuals receive the rank of 1. The optimization algorithm converges when change in average Pareto spread falls below a certain limit over several generations (stall generations).

In MATLAB, GA employs three different operators named selection, crossover, and mutation whose implementations are customized for this software. In the selection process, individuals in a population are selected for the next generation. It is based on their rank as well as their distance from each other. In other words, for individuals with the same rank, farther individuals are privileged in order to preserve diversity, which is very important to maintain a successful search. After selection, individuals are divided into two groups; one group evolves through crossover and the other group mutates per se. In crossover, a new individual is formed by combination of two parents. This newly formed individual is called offspring or child, which inherits information from both parents. On the other hand, in the mutation operation, random changes occur in the genes level of single individuals. Mutation reintroduces genetic diversity back into the population and assists the search to escape from local optima.

The optimizer calls the model with a set of decision variables as individuals and receives the process performance indicators in return at the end of each run. In the simulation studies, cyclic steady state can be achieved quickly, but for more assurance, several cycles of operations are considered as shown in Fig. 2.2(a). See Chapter 6 for a discussion on the implications of non-steady state operation.

5.3.2 Numerical methods

The model equations comprise partial differential equations (PDEs), which are discretized in space using third-order weighted essentially non-oscillatory (WENO) scheme as introduced in Chapter 3. It is more convenient than other alternatives (e.g., van Leer flux limiter [61]) when axial dispersion is significant and as a result, sharp fronts are smoothed. The resulting set of ordinary differential equations (ODEs) is solved by the method of lines. Among different ODE solvers which we tested, Adams-Bashforth-Moulton PECE solver [85] (ode113) seemed to be the most satisfactory in terms of handling computationally intensive problems. The simulation parameters are given in Table 5.3.

Table 5.3: Simulation parameters used in MATLAB

Parameter	Value
ODE solver	Adams-Bashforth-Moulton [85]
Absolute integration tolerance	10^{-6}
Relative integration tolerance	10^{-4}
Initial time step	0.001 s
Number of grid points	400

The discretized equations were compiled in C programming language, but embedded in MATLAB environment. Moreover, GA can call functions in parallel. As a result, using embedded C codes and parallel-processing techniques on multi-core processors, the computational speed could be boosted drastically. The convergence typically occurs in less than an hour on a Dell Precision T3500 computer with an Intel Xeon 2.93 GHz, eight-core CPU and 3 GB of memory.

Moreover, mass balance equations must be solved for accumulation in the intermediate vials. As a result, purity, recovery, productivity, and desorbent requirement are calculated in each cycle as average values. Calculations are restarted when a new cycle emerges.

5.4 Results and discussion

5.4.1 Improved single-column chromatography

The results of four case studies with different purity and recovery constraints are reported here as summarized in Table 5.4. The optimization results are presented in terms of Pareto fronts. Furthermore, the effects of decision variables on the performance indicators are analyzed and presented.

Table 5.4: Purity and recovery requirement constraints for optimization case studies.

Case	Purity	Recovery
A	90 %	85 %
B	95 %	90 %
C	98 %	95 %
D	99.9 %	98 %

5.4.2 Pareto fronts

The optimal operating points obtained as Pareto fronts are shown in Fig. 5.1 where the horizontal axis and vertical axis correspond to productivity and desorbent requirement, respectively. Any operating point that falls in the left and above part of a Pareto front is suboptimal. On the other hand, any point to the right and below of any Pareto front is inaccessible. It is clear from Fig. 5.1 that as we move from less stringent constraints (case A, P=90%, Y=85%) to more stringent constraints (case D, P=99.9%, Y=98%), the Pareto curves move up and left indicating higher desorbent requirement and lower productivity. Apart from this shift, the Pareto fronts become steeper, indicating that at higher purity and recovery values, any increase in productivity requires a greater increase in desorbent requirement compared to less stringent cases.

Across these case studies, a 10% decrease in purity constraint can boost productivity by about a factor of six, while it can only reduce desorbent requirement by about a factor of two. Therefore, while there is a large degree of freedom on productivity, in comparison, desorbent requirement is limited to a narrow range of values.

There are discontinuous sections observed in some of the Pareto fronts. This can be explained by looking at the entire feasible population. In the discontinuous regions, the population passes through a maximum when Dr is plotted vs. Pr . The maximum point and its neighboring points are dominated by the right hand section of the Pareto front and therefore they do not appear as a part of optimal points. This phenomenon may result in a wide gap in the final Pareto front. This reiterates the necessity of observing good level of diversity during optimization to ensure that all discontinuous sections were explored.

Figure 5.1: Pareto fronts as productivity and desorbent requirement under different purity and recovery constraints. Case A: P=90%, Y=85%, case B: P=95%, Y=90%, case C: P=98%, Y=95%, and case D: P=99.9%, Y=98%.

5.4.3 Elution profiles

In Figs. 5.2 and 5.3, the simulated chromatograms are given for the two extreme points of the Pareto fronts of case A and case D, respectively. It was observed that for case study A, there is significant amount of overlapping between peaks of two consecutive cycles. For case study D however, overlapping diminishes and we have almost base-line separation. This implies that an overlapping scheme is favorable for reduced-purity and recovery conditions as the optimizing algorithm adopts majority of solution points from this region of operation.

5.4.4 Effects of decision variables

In Figs. 5.4(a)-5.5(b), the effects of decision variables on productivity and desorbent requirement for cases A and D are shown. The results of cases B and C show similar pattern. Since it has a clear relation with productivity and desorbent requirement, we have also reported the effect of throughput (Eq. 5.20), which is a function of three independent decision variables namely, feed concentration, cycle time, and injection volume

$$T_F = \frac{c_T^F V_{inj}}{t_{cy}} \quad (5.20)$$

For a better insight, the Pareto results of case study D given in previous figures are summarized in Table 5.5. These points are all the subset of feasible solutions yielding the best values of objective functions. The results of other case studies are not shown here for brevity.

(a)

(b)

Figure 5.2: Chromatograms of case A ($P=90\%$, $Y=85\%$): (a) Left most point of the Pareto front; (b) Right most point of the Pareto front.

(a)

(b)

Figure 5.3: Chromatograms of case D ($P=99.9\%$, $Y=98\%$): (a) Left most point of the Pareto front; (b) Right most point of the Pareto front.

Table 5.5: Decision variables and objective functions of the Pareto front for case D.

Pr (g/(min g))	Dr (L/g)	V_{inj} (μ L)	t_{cy} (s)	Q^D (mL/min)	c_T^F (g/L)	dt_{c1} (s)	dt_{c2} (s)	dt_{c3} (s)
0.0070	0.228	1341	83.6	6.7	35.0	18.5	2.9	61.8
0.0070	0.228	1341	83.6	6.7	35.0	18.5	2.9	61.8
0.0074	0.232	1338	79.2	7.2	34.9	17.4	2.6	58.2
0.0075	0.235	1326	77.4	7.4	34.9	17.0	2.5	56.2
0.0077	0.238	1311	75.0	7.7	34.9	16.4	2.4	53.5
0.0079	0.241	1299	72.1	8.0	35.0	15.8	2.3	53.3
0.0083	0.244	1290	67.8	8.6	34.9	14.8	2.2	49.2
0.0087	0.258	1293	62.9	9.5	33.7	13.6	2.2	46.8
0.0091	0.270	1290	58.8	10.4	33.1	12.5	2.0	42.2
0.0091	0.270	1290	58.8	10.4	33.1	12.5	2.0	42.2
0.0107	0.297	1151	47.1	13.8	35.0	9.4	1.9	35.4
0.0138	0.302	1057	33.3	18.2	34.9	7.4	1.5	23.8

Fig. 5.4(a) shows that feed concentration has a significant effect on the performance indicators. Most of the optimal points are located in a narrow range near the solubility limit. This is because when feed concentration increases, productivity increases and desorbent requirement decreases thereby acting in the same direction in terms of improving the objectives. In fact, feed concentration acts mostly as a scaling factor; it increases the loading, but has a less significant effect on peak width.

The effect of injection volume is shown in Fig. 5.4(b). In the nonlinear range of operation and in the presence of non-ideal effects, injection volume may not be fixed as opposed to what we observed in Chapter 4, though it has a relatively narrow range of variation. Besides, as purity and recovery requirements rise, lower injection volumes are favored.

Fig. 5.4(c) shows that productivity and desorbent requirement monotonically fall as cycle time increases. The effect on productivity can be readily explained by Eq. 5.3. However, the effect of cycle time on desorbent requirement can be explained when variations in desorbent flow rate and cycle time are observed together. In fact, cycle time and desorbent flow rate compensate the effect of each other as the term $Q^D t_{cy}$ which appears in the definition of desorbent requirement (Eq. 5.4), has a narrow range of variation with a small negative slope once plotted vs. cycle time.

Fig. 5.4(d) shows that throughput, which is a combination of three decision variables as described in Eq. 5.20, has a linear relation with Pr . However, because all the three combined variables are constrained, they have to be taken as independent decision variables for optimization.

Eq. 5.4 can be written in terms of throughput

$$Dr = \frac{Q^D}{T_F} + \frac{1}{c_T^F} \quad (5.21)$$

The pattern observed in Fig. 5.4(d) shows that unlike what is inferred from Eq. 5.21, desorbent requirement increases as throughput increases because the effect of desorbent flow rate completely dominates the effect of throughput. Therefore, these effects must be understood in a holistic way.

The increase in desorbent requirement with increasing desorbent flow rate may look

intuitive as it can be inferred from Eq. 5.4 and seen in Fig. 5.4(e). However, apart from what Eq. 5.4 implies, the adverse effect of flow rate on the column efficiency must also be accounted for. This means that at higher flow rates, a larger elution volume is required for a fixed resolution.

On the other hand, an increase in Pr with increasing Q^D is due to the fact that for a certain purity and recovery requirement, larger desorbent flow rate allows for shorter cycle time and as a result, higher productivity.

The primary role of the cut intervals is to guarantee purity and recovery with the ultimate objectives of increasing productivity and decreasing desorbent requirement. For a specific purity and recovery requirements, the first and third cut intervals vary in a similar fashion as of the cycle time as shown in Fig. 5.5. Although due to the tailing effect of the Langmuir-type isotherm, third cut interval constitutes a relatively larger portion of the cycle time. As a result, the more retained product fraction (rich in component A) is less concentrated than the less retained one (rich in component B).

In contrast to first and third intervals, second cut interval is determined such that specifications of product fraction A are satisfied at minimal cycle time and desorbent flow rate. Actually, second fraction is primarily the overlapped part of the concentration profiles of products B and A. A low value of second cut interval is therefore beneficial for reducing the loss of product A as it increases recovery. It is also beneficial for increasing productivity as it decreases the cycle time, which is observed in Fig. 5.4(f) where it is clustered towards its lower limit. A higher value of second cut interval is observed for case study D compared to case study A. This is expected since the product purity requirement is more stringent in the former case.

5.4.5 Simulated moving bed

For comparison, we have also presented the results of a closed-loop SMB process equivalent to the ISCC process. The overall length and diameter of the SMB unit is the same as of the ISCC. A 1:2:2:1 configuration is assumed for this unit. Objective functions are defined in a similar fashion as of the ISCC

$$Pr = \frac{c_T^F Q^F}{m_{ad}} \quad (5.22)$$

$$Dr = \frac{Q^F + Q^D}{c_T^F Q^F} \quad (5.23)$$

and the decision variables are m_1 , m_2 , m_3 , m_4 , t^* , and c_T^F [29].

Process constraints and ranges of decision variables are also the same as what was reported for ISCC in Table 5.2. Optimization of the SMB unit was done only under the highest purity and recovery requirements (i.e., $P \geq 99.9\%$). The Pareto front of the SMB process shown in Fig. 5.6, along with that of ISCC under comparable conditions (i.e., $P = 99.9\%$, $Y = 99.5\%$), illustrates that the SMB process significantly outperforms the ISCC process.

Figure 5.4: Effects of decision variables on productivity and desorbent requirement: (a) feed concentration; (b) injection volume; (c) cycle time; (d) throughput; (e) desorbent flow rate; (f) second cut interval (case A: P=90%, Y=85%, case D: P=99.9%, Y=98%).

Figure 5.5: Effects of decision variables on productivity and desorbent requirement: (a) first cut interval; (b) third cut interval (case A: P=90%, Y=85%, case D: P=99.9%, Y=98%).

Figure 5.6: Pareto fronts of ISCC and SMB.

5.5 Interim conclusion

We have presented an improved single-column chromatographic (ISCC) process for separation of mixture of enantiomers with an online monitoring system that has provisions for future use of an online optimizing controller. This provides the basis for reaping the full potential of a single-column process that adopts cyclic injection.

The ISCC process was optimized over a wide range of operating parameters namely, injection volume, cycle time, desorbent flow rate, feed concentration, and three cut intervals with the objectives of maximizing productivity and minimizing desorbent requirement for different product purity and recovery specifications. It is apparent that traditional experimental optimization techniques could not handle the complexity of this problem. Therefore, the resulting solutions were obtained through genetic algorithm and presented as a set of Pareto-optimal points providing a way for quantification of the best achievable sets of productivity and desorbent requirement values. Depending on economic and/or environmental considerations, the end user is able to make an informed choice of a suitable operating point from Pareto set. Calculation of gain in productivity and saving in desorbent consumption under less stringent product specification was also facilitated through this work.

The relative contribution of the decision variables were ascertained through the study of their effects on the performance indicators. Productivity was found to be a linear function of throughput, which comprises three independent decision variables namely, feed concentration, injection volume, and cycle time. However, desorbent requirement expresses a complex relation with throughput. The importance of the second cut interval of fraction collection which primarily regulates purity and recovery values, was also demonstrated.

The results demonstrated that overlapped peaks (either from the same cycle or from adjacent cycles) can be admitted advantageously to enhance productivity and decrease desorbent requirement. The operability at such a point must be guaranteed by using an online optimizing controller, which is discussed in Chapter 6.

Finally, the optimized ISCC process was compared with an optimized SMB process under pure and almost fully recovered products. Results confirmed the advantages of continuous SMB process.

Nomenclature

c	fluid phase concentration of solute [g/L]
D	column diameter [cm]
D_{ax}	axial dispersion coefficient [cm^2/s]
Dr	desorbent requirement [L/g]
d_P	particles diameter [μm]
dt_{ci}	cut intervals [s]
H_i	Henry constant of species i [-]
K_i	equilibrium constant in Langmuir isotherm of species i [L/g]
k_l	liquid film mass transfer coefficient [1/s]
L	column length [cm]
m_{ad}	mass of adsorbent [g]
m_j	Dimensionless flow-rate ratio [-]
n	solid phase concentration of solute [g/L]
P	purity [%]
Pe	Peclet number [-]
Pr	productivity [g/(min g)]
ΔP	pressure drop [bar]
Q	volumetric flow rate [mL/min]
Re	Reynolds number [-]
t^*	switching time [s]
t_{cy}	cycle time [s]
t_{sc}	start of cycle [s]
T_F	throughput [g/min]
u	superficial velocity [cm/s]
v	interstitial velocity [cm/s]
V_{inj}	injection volume [μL]
Y	recovery [%]

Greek letters

ε	overall void fraction of column [-]
ϕ	resistance parameter [-]
λ_{pt}	penalty factor [-]
μ	viscosity [Pa.s]

Subscripts and superscripts

<i>ad</i>	adsorbent
<i>ax</i>	axial
<i>A</i>	more retained component (S)-(+)-guaifenesin
<i>B</i>	less retained component (R)-(–)-guaifenesin
<i>D</i>	desorbent
<i>E</i>	extract
<i>F</i>	feed
<i>i</i>	component index
<i>inj</i>	injection
<i>min</i>	minimum
<i>max</i>	maximum
<i>R</i>	raffinate

Chapter 6

Model Predictive Control of the ISCC Process

Optimal operation of chemical processes is typically described as a dynamic optimization problem. In such problems, there is an economic objective function that must be minimized (or maximized) over time under the effects of a controlling scheme. There are two paradigms in implementing the optimal solution of such problems [86]:

Paradigm 1: The optimizing controller is implemented online and measurements are basically used to update/estimate the underlying dynamic model. The model can be of any level of complexity. The optimization problem is solved for every time step or at least when new measurement arrives.

Paradigm 2: Pre-computed solutions are prepared in an offline manner. The model uncertainties and disturbances can be taken into account through robust modeling or indirect measurements along with feedback control schemes.

Our proposed approach and other conventional MPC schemes generally fall under the category of paradigm 1, which has been widely used in research and industry in the past 30 years [17, 18, 19]. Although these schemes have a lot to share with offline, single-objective optimization techniques, in practice, they are completely different. Offline optimization techniques like what we implemented in Chapter 5 suffer from the fact that they are blind toward model uncertainties and unmeasured disturbances. Therefore, such solutions are inevitably infeasible or suboptimal in the face of actual operation.

It must be noted that there have been recent efforts to develop optimization schemes in the realm of paradigm 2 as they offer advantages including robustness, simplicity and reduced cost of modeling, implementation, and maintenance [86, 87, 88].

MPC is popular in the chemical and pharmaceutical industries including applications of chromatographic separation in particular for continuous processes such as SMB [6, 18, 20, 21]. Although there is a few number of applications of MPC in batch chromatographic separation processes [22], their intrinsic nonlinearity, stringent product specifications, and large number of input-output variables necessitate application of an online optimizing control algorithm and make it a challenging problem.

Actually, regarding disturbance effects, the same rational for continuous chromatographic separation processes applies to batch operation; temperature change, packing aging, change in desorbent composition, etc. may drift the process away from its correct optimal operating point, and therefore provisions must be made to bring the

process back to the updated optimal conditions. It is apparent that there must be a mechanism for handling the effects of uncertainties and disturbances in solving the optimization problem.

In the conventional model predictive control scheme, the objective is to optimize a performance function over a prediction horizon by means of deciding on the values of manipulated variables over a control horizon. However, only the first elements of the optimized vector of manipulated variables are applied and the rest are discarded. This approach is known as receding horizon strategy [21]. The same procedure is carried out at the next time step, meaning that a new optimization problem has to be solved for every time step.

The predictive action is realized via utilizing a model, which can be a detailed one or just a linear empirical model in a suitable form such as observable state space representation or an autoregressive with exogenous input (ARX) model [89].

In the conventional MPC approach, provisions must be made to capture the effects of disturbances and model uncertainties that occur over time. For this purpose, with the help of measurements, one can utilize an online state estimator or alternatively, the model is recursively updated over time. In this work we use a time-varying Kalman filter as a state estimator to reduce the effects of disturbances and uncertainties [90, 91].

We have implemented a ‘cycle to cycle’ MPC scheme for the proposed ISCC process (See Chapter 2 for detailed description of the process). Although this process is operated in batch mode, with proper formulation of the outputs and inputs, it can reach cyclic steady state for consecutive runs similar to continuous processes. In fact, the idea behind this formulation is to provide less frequent but more accurate information to the controller. In Chapter 2, we described how to obtain accurate data per cycle via using an efficient online monitoring system, which can measure average purity and recovery values. Therefore, at the first glance, the ‘cycle to cycle’ MPC scheme suits the available monitoring system. However, the detailed process model must be reduced to an appropriate form to receive average values of inputs per cycle and then to return the prediction of averaged process outputs.

In the following, we first explain how the problem must be reformulated for unsteady state operation. Then we establish the input-output relations, we describe the identification and state-estimation procedures, and then implement the ‘cycle to cycle’ MPC scheme, which is based on quadratic programming (QP). The controller formulation is discussed in Section 6.3.

6.1 Problem statement

6.1.1 Peak detection method

A typical chromatogram is shown in Fig. 6.1 for the case when there is a sudden change in the desorbent flow rate. Similar to steady state operation, the start of collection is detected by the UV detector as the rising shoulder of the first peak elutes, and hence it is considered as the start of the first cycle. However, unlike steady state operation, the consecutive start points cannot be calculated with respect to this point as the actual cycle time may vary due to change in flow rate or other parameters as can be seen in Fig. 6.1. Therefore, a new fraction collection strategy must have been

envisaged.

Peak detection techniques are well established in the field of chromatography [92, 93]. They can be utilized to identify both peaks and valleys. We propose a simple but effective method here based on the detection of rising and falling shoulders. Assuming that the detector signal $y_{UV}(i)$ is available in discrete form, we define the following condition for valley detection

$$S_v(i) = y_{UV}(i) > y_{UV}(i-1) \wedge y_{UV}(i-1) > y_{UV}(i-2) \wedge y_{UV}(i-2) > y_{UV}(i-3) \quad (6.1)$$

and for peak detection, we define

$$S_p(i) = y_{UV}(i) < y_{UV}(i-1) \wedge y_{UV}(i-1) < y_{UV}(i-2) \wedge y_{UV}(i-2) < y_{UV}(i-3) \quad (6.2)$$

The first time S_v becomes true, is considered a valley, and the first time S_p becomes true, is considered a peak. The two conditions must be checked for every single data point or at least for a cluster of data points. They are reset once any of them changes value. We need to detect all peaks and valleys in order to identify the actual cycles. In each cycle, two peaks and two valleys must be detected. The end of cycle is the time when the second valley emerges from the column.

Figure 6.1: Simulated chromatograms for a sudden change in flow rate from 17.0 to 27.0 mL/min at 40 s after startup. The actual cycle time for cycle 2 drops from 30 to 20 s and then returns to its nominal value, 30 s. The injection cycle time is 30 s.

6.1.2 Plant inputs

Injection volume, desorbent flow rate, and three cut intervals are taken as manipulated variables. The three cut intervals have static effects in the sense that they affect only one cycle of the operation. However, injection volume and desorbent flow rate have dynamic effects over two or more cycles. Based on an in depth preliminary analysis, it was decided to incorporate all the decision variables in the MPC scheme.

6.1.3 Plant outputs

The plant outputs are purity, recovery, productivity, and desorbent requirement, all averaged per cycle. As the inputs may directly affect the outputs (direct feedthrough),

we have assigned one cycle delay between them to prevent solution problems arising in the MPC scheme.

In fact, we have formulated a performance function as a new output, which represents the profitability of the operation

$$F_{PD} = \lambda_1 (Pr - Pr_s) - \lambda_2 (Dr - Dr_s) \quad (6.3)$$

Pr_s and Dr_s are steady state values around which the process is linearized. The advantage of this definition is that the steady state offset is automatically removed from this output variable. λ_1 and λ_2 are two weight factors properly set at 50 and 5, respectively.

The four other variables are average purity and recovery values of components A and B as defined in Chapter 5. The input-output relations are depicted in Fig. 6.2.

Figure 6.2: Schematic block diagram of the ‘cycle to cycle’ MPC scheme.

6.1.4 Disturbances

Temperature change, packing aging, change in desorbent composition or feed concentration, etc., these are the everyday hassles in chromatographic separation and have more or less important effects on the process performance. Any controller scheme must be robust enough to tackle with such disturbances. Our proposed MPC scheme provides feedforward action for measured disturbances and feedback compensation for unmeasured disturbances, while the state estimator tries to reduce prediction error. All actions are carried out in an online manner. In contrast, as mentioned earlier, there are also other approaches that try to compensate for disturbances by robust design of offline MPC schemes [87].

Constraint violation is not the only concern when facing disturbances. From profit and loss point of view, a disturbance may drift the process away from its optimal operating point and therefore, provisions must be made to guide the process toward new optimal operating points, while fulfilling the product and process constraints. This is indeed an important feature of MPC provided that it is set up and implemented properly.

In this work, we have considered change in feed concentration and Henry constants as unmeasured disturbances, which occur in the form of step changes. Offline optimization studies have shown that the optimal operating points vary when these variables drift so we expect the controller to quickly recover the performance function (F_{PD}) while maintaining the constraints.

The MPC scheme requires predictions of the prospect of process variations. For a better estimation, the nature of disturbances must be known as a priori knowledge.

The above mentioned disturbances affect the process outputs in a complex way. On the other hand, the measurement is assumed to be corrupted with white noise with a unit variance. This information is provided to the state estimator as discussed further in Section 6.4.

It must be noted that cycle time is fixed in this work by default. However, the actual cycle time may vary due to the effect of change in desorbent flow rate or other inputs as explained earlier in Section 6.1.1. This may also complicate the process response as an additional unmeasured disturbance.

6.2 System identification

Although MPC needs a reliable model, it is advantageous to design the controller in such a way that it does not hinge on system characteristic information (e.g., isotherm parameters and physical properties) as much as possible [94]. The reason behind this argument is the computational burden of updating complex models, which may make them futile in practice. Therefore, majority of the recent applications of MPC in preparative chromatography have utilized simplified models [21, 22, 95].

There are generally two approaches for obtaining simplified models: model reduction techniques [96] and identification methods [89]. In our work, we fix the structure of the empirical model as a priori knowledge based on the identification results. The identification task can be done based on either running a detailed model or collecting experimental data in an offline manner. Once this task has been accomplished successfully, no other characteristic information is required for closed-loop operation.

We have used a linear ARX model to empirically relate the inputs, V_{inj} , Q^D , and dtc_i to the outputs F_{PD} , P_i , and Y_i as defined earlier. The ARX model can be defined as

$$A(q)y(t) = B(q)u(t) + e(t) \quad (6.4)$$

where q is the time-shift operator equal to one cycle. $A(q)$ is defined as

$$A(q) = I + A_1q^{-1} + \dots + A_{n_a}q^{-n_a} \quad (6.5)$$

and $B(q)$ is defined as

$$B(q) = B_1q^{-n_k} + B_2q^{-1-n_k} + \dots + B_{n_b}q^{-n_b-n_k+1} \quad (6.6)$$

where n_a is the number of poles, n_b is the number of zeros plus 1, and n_k is the time delay [89, 97]. For a multi-input multi-output (MIMO) system, each element of $A(q)$ and $B(q)$ is a matrix itself. Moreover, outputs can also affect each other. However, writing the equations in the above mentioned form implies that in contrast to previous outputs, the current instances of outputs ($y(t)$ s) cannot be interrelated because $A(q)$ initiates with identity matrix.

We used system identification toolbox of MATLAB 2010a. The toolbox offers several identification techniques such as least squares (LS), instrumental variable (IV), subspace identification, prediction-error method (PEM), etc. Some of the models have the option of selecting between more than one identification method [97]. We used least squares and instrumental variable on the ARX model.

The problem is formulated so as to minimize the error between simulated and measured outputs by finding the best estimate of model parameters. User can decide on

the type and order of the model as well as the solution technique. Our final selection was done based on the best fit, which is defined as

$$\text{Best Fit} = \left(1 - \frac{|y - \hat{y}|}{|y - \bar{y}|} \right) \times 100 \quad (6.7)$$

y is the measured output, $\hat{y}$ is the simulated output and $\bar{y}$ is its average. A perfect fit yields a value of 100%.

Using a virtual plant, the identification procedure was carried out over a set of 180 cycles randomly-generated inputs around an optimal point obtained through offline optimization as given in Table 6.1. The results were validated via 52 cycles of independent data points as shown in Fig. 6.3. The validation data is not involved in parameter estimation. This approach lowers the risk of overfitting the data.

Table 6.1: Linearization point as the basis for system identification and the range of inputs. Note that t_{cy} and c_T^F are not manipulated variables.

Parameter	Value	Parameter	Value	Range
P_A^s	98 %	V_{inj}	1758.7 μL	$\pm 500 \mu\text{L}$
P_B^s	98 %	t_{cy}	30.0 s	-
Y_A^s	95.5 %	Q^D	17.88 mL/min	$\pm 3 \text{ mL/min}$
Y_B^s	95.1 %	c_T^F	34.91 g/L	-
Pr_s	0.0254 g/(min g)	dt_{c1}	7.10 s	$\pm 1 \text{ s}$
Dr_s	0.174 L/g	dt_{c2}	0.72 s	$\pm 0.3 \text{ s}$
		dt_{c3}	21.75 s	$\pm 2 \text{ s}$

The simulation parameters are the same as offline optimization, which was discussed in Chapter 5. The main exception is the peak detection technique described in Section 6.1.1 for handling varying cycle times.

The fit values are given in Table 6.2 both for the ARX model and also for a state space one, which is given here for comparison. The ARX model is obtained by least squares and the state space model is obtained by subspace identification. The instrumental variable method failed to converge to any acceptable set of parameters. We also ensured that model residuals are within acceptable ranges. Based on the results the ARX model is simpler and in general more accurate than the state space one. For the ARX model $n_a = 3$, $n_b = 4$, $n_k = 1$. The order of the state space model is 10 with one delay from all inputs. Assigning other values for delays seriously deteriorates the estimation results of the models. This finding also suggests that only the first incoming cycle is heavily affected by change in inputs.

Table 6.2: Best-fit values (in percent) for the identified ARX model and state space (SS) model. For the ARX model $n_a = 3$, $n_b = 4$, $n_k = 1$. The order of the SS model is 10 with one delay from inputs.

Output	ARX	SS
F_{PD}	91.0	31.6
P_A	64.4	62.0
P_B	60.1	60.7
Y_A	67.8	68.6
Y_B	69.1	68.3

In our approach any identified model is eventually converted to a state space representation inside the controller structure. Therefore, the states may not represent any meaningful variable though the inputs and outputs remain unchanged as given in Sections 6.1.2 and 6.1.3, respectively.

6.3 Model predictive control

The backbone of a model predictive control scheme relies on solving a dynamic optimization problem. The time domains from which output and input samples are involved in the solution are called prediction horizon (p) and control horizon (m), respectively. The optimization problem can be formulated as follows

$$\Delta u(k|k), \dots, \Delta u(m-1+k|k), \epsilon \left\{ \sum_{i=0}^{p-1} \left(\sum_{j=1}^{n_y} |w_{i+1,j}^y (y_j(k+i+1|k) - r_j(k+i+1))|^2 + \sum_{j=1}^{n_u} |w_{i,j}^{\Delta u} \Delta u_j(k+i|k)|^2 + \sum_{j=1}^{n_u} |w_{i,j}^u (u_j(k+i|k) - u_{jtarget}(k+i))|^2 \right) + \rho_\epsilon \epsilon^2 \right\} \quad (6.8)$$

subject to the following constraints

$$u_{jmin}(i) - \epsilon V_{jmin}^u(i) \leq u_j(k+i|k) \leq u_{jmax}(i) + \epsilon V_{jmax}^u(i) \quad (6.9)$$

$$\Delta u_{jmin}(i) - \epsilon V_{jmin}^{\Delta u}(i) \leq \Delta u_j(k+i|k) \leq \Delta u_{jmax}(i) + \epsilon V_{jmax}^{\Delta u}(i) \quad (6.10)$$

$$y_{jmin}(i) - \epsilon V_{jmin}^y(i) \leq y_j(k+i|k) \leq y_{jmax}(i) + \epsilon V_{jmax}^y(i) \quad (6.11)$$

for $i = 0, \dots, p-1$, and

$$\epsilon \geq 0 \quad (6.12)$$

u and y are the array of inputs and outputs, respectively. The subscript j is the j th element of a vector. The expression $k+i|k$ means predicted value at time $k+i$ based on the information available at time k . $r(k)$ is the reference (setpoint) trajectory at time k , which can be a function of time. $u_{jtarget}(k)$ is the setpoint value for input j . The controller tries to minimize the difference between this value and the j th input if it is necessary to fix any of the inputs.

$w_{i,j}$ values are weights associated with y , u , and Δu to adjust the relative importance of their respective variables in the objective function defined above. The weight ρ_ϵ regulates the importance of violating the constraints. The slack variable, ϵ which is a positive scalar here, takes the value of the largest constraint violation. Also, by default

$$\rho_\epsilon = 10^5 \max \{w_{i,j}^{\Delta u}, w_{i,j}^u, w_{i,j}^y\} \quad (6.13)$$

The equal concern for relaxation (ECR) vectors $V_{min}(i)$ and $V_{max}(i)$, are nonnegative and reflect the tolerance for violating their corresponding constraints. The larger the

Figure 6.3: Validation results of the identified ARX model around the point given in Table 6.1; the outputs are: (a) F_{PD} ; (b) P_A ; (c) P_B ; (d) Y_A ; (e) Y_B . Mean values are removed from the outputs for identification.

value of ECR is, the less stringent the respective constraint is. A zero value for ECR means a hard constraint that must never be violated [98].

The manipulated variables or outputs of the controller are injection volume, desorbent flow rate, and three cut intervals. The measured outputs are performance function F_{PD} , purity, and recovery for both components, which are retrieved from the online monitoring system at the end of each cycle of analysis.

Numerical values associated with the inputs and outputs in the MPC structure are given in Table 6.3. No constraint is imposed on the outputs through the MPC design. Instead, they are controlled by enforcing setpoints. Prediction horizon, control horizon, and other MPC design parameters are summarized in Table 6.4.

Table 6.3: Numerical values associated with the inputs and outputs in MPC structure. Note that ECR is the same for lower and upper bounds. Rate ranges and rate weights are related to the constraints on Δu .

Parameter	Range	Rate range	Weight	Rate weight	ECR
V_{inj}	$\pm 500 \mu\text{L}$	± 50	0.005	0.1	2×10^7
Q^D	$\pm 3 \text{ mL/min}$	± 0.01	50	50	2×10^7
dt_{c1}	$\pm 1 \text{ s}$	± 0.05	10	10	2×10^7
dt_{c2}	$\pm 0.5 \text{ s}$	± 0.02	50	50	2×10^7
dt_{c3}	$\pm 2 \text{ s}$	± 0.05	50	200	2×10^7
F_{PD}	$\pm \infty$	NA	0.01	NA	2×10^7
P_A	$\pm \infty$	NA	0.5	NA	2×10^7
P_B	$\pm \infty$	NA	0.5	NA	2×10^7
Y_A	$\pm \infty$	NA	1	NA	2×10^7
Y_B	$\pm \infty$	NA	1	NA	2×10^7

The prediction horizon and control horizon are selected based on two criteria to reap the full potential of MPC: first, the prediction horizon must be far greater than plant pure time delay ($p \gg d$). Second, the control horizon must be much smaller than the difference between the prediction horizon and plant pure time delay ($m \ll p - d$) [98].

Table 6.4: Prediction horizon, control horizon, and other MPC design parameters.

Parameter	Value
Prediction horizon	10
Control horizon	2
Manipulated variables	5
Measured disturbances	0
Measured outputs	5
Unmeasured outputs	0

It must be emphasized that the reference values, $r(k)$ in these formulations refer to the plant outputs in the deviation form. F_{PD} is defined in such a way that it is zero at the steady state point close to the linearization point, and therefore it can be readily supplied to the controller without calculating the deviation variable. However, the steady state values must be subtracted from all inputs and four other outputs, namely purity and recovery values in order to avoid a bump when the controller is switched on.

The model predictive toolbox of MATLAB 2010a was used for implementing the MPC scheme. A virtual plant was implemented in Simulink, which has the capability of handling hybrid—continuous and discrete—systems. The numerical techniques are similar to those used for offline optimization, though as mentioned in Section 6.1.1, the fraction collection strategy is different here in order to cope with the time varying cycle time. We stress again that although the cycle time for injection is fixed, which is the same as the sampling time of the controller, the actual cycle time may fluctuate around its nominal value under the effect of change in desorbent flow rate or other inputs.

A discrete time delay was implemented after the controller block in simulation in order to break the algebraic loop caused for closed-loop modeling. This delay can also be accounted as measurement time delay in case the online monitoring system cannot return the measurement results in one cycle.

6.4 Online state estimation and prediction

The advantage of using a state estimator with filtering effect is twofold; on one hand it reduces the noise effect on the outputs and on the other hand it compensates the effects of model uncertainties or disturbances, both reducing the difference between measured and calculated outputs. These necessitate that a priori knowledge of the noise and disturbances must be known beforehand. For larger presumed noise values, the estimator infers that discrepancies are mainly measurement noise not model uncertainties or disturbances and vice versa.

Before jumping to the mathematics of state estimation. It is useful to give an illustrative description of how an identified model is used for state estimation and prediction. Focusing on the conventional type of MPC and linear models, the offline-identified model provides the nominal information (e.g., state space matrices), which is then used in the state estimator to obtain an update of estimated states with the help of measured outputs. Finally the estimated states are used to predict future variations of outputs. The predicted output values are utilized to solve the MPC optimization problem. This is illustrated in Fig. 6.4. It must be noted that what the state estimator sends to the controller are the predicted outputs comprising the prediction horizon.

Figure 6.4: Hierarchical processes of offline identification and online estimation-prediction.

A time-varying Kalman filter, which is a generalization of steady state Kalman filter,

is used here as state estimator in conjunction with the controller. The target is to minimize the estimation error covariance

$$P(k|k) = E \left(\{x(k) - \hat{x}(k|k)\} \{x(k) - \hat{x}(k|k)\}^T \right) \quad (6.14)$$

Given the plant state and measurement equations

$$\begin{aligned} x(k) &= Ax(k) + Bu(k) + Gw(k) \\ y(k) &= Cx(k) + v(k) \end{aligned} \quad (6.15)$$

the time-varying Kalman filter is given in two recursive steps:

- **Measurement update**

$$\begin{aligned} \hat{x}(k|k) &= \hat{x}(k|k-1) + M(k) (y(k) - C\hat{x}(k|k-1)) \\ M(k) &= P(k|k-1)C^T (R(k) + CP(k|k-1)C^T)^{-1} \\ P(k|k) &= (I - M(k)C) P(k|k-1) \end{aligned} \quad (6.16)$$

where $\hat{x}(k|k-1)$ is the estimate of $x(k)$ based on $y(k-1)$ and $\hat{x}(k|k)$ is the updated estimate based on the last measurement $y(k)$. The innovation gain matrix $M(k)$ is designed by solving a discrete Riccati equation.

- **Time update**

$$\begin{aligned} \hat{x}(k+1|k) &= A\hat{x}(k|k) + Bu(k) \\ P(k+1|k) &= AP(k|k)A^T + GQ(k)G^T \end{aligned} \quad (6.17)$$

with auxiliary information

$$\begin{aligned} Q(k) &= E (w(k)w(k)^T) \\ R(k) &= E (v(k)v(k)^T) \\ P(k|k-1) &= E \left(\{x(k) - \hat{x}(k|k-1)\} \{x(k) - \hat{x}(k|k-1)\}^T \right) \end{aligned} \quad (6.18)$$

w and v are additive noises on the inputs and outputs, respectively. The noise covariance matrices Q and R must be known a priori.

The initial conditions must also be given for both the state estimates $\hat{x}(k|.)$ and the error covariance matrix $P(k|.)$. They are updated over time in a recursive manner to perform the filtering.

The MPC toolbox of MATLAB accepts three types of disturbances: Input disturbances, output disturbances, and measurement noise [90, 91, 98]. As mentioned in Section 6.1.4, a white noise with unit variance is added to the outputs as measurement noise. Output disturbances were set to zero and input disturbances were set at a unit step. This latter choice is based on the assumption that the disturbances (e.g., change in feed concentration) affect the outputs through system states. In other words, they do not directly affect the outputs. In practice, no significant improvement was observed upon adding other types of disturbances to inputs and outputs in simulation studies given in Section 6.5.

Predicted outputs are calculated from the following formula

$$y(k+i|k) = S_x \hat{x}(k|k) + S_u \Delta u(k+i-1) \quad (6.19)$$

for $i = 1, \dots, p$.

The prediction matrices S_x and S_u are built by successive substitution of states and outputs in Eq. 6.15 assuming w and v are both zero.

It is worthy of attention that the MPC toolbox implements a step disturbance by integrating the white noise, which is internally converted to a state space model. The original state space model is then augmented with the input and output disturbance and noise models. All of the augmented states are updated in the state estimator. The augmented model must be observable for the state estimation design to succeed.

6.5 Results and discussion

In this section, the results of three case studies one for setpoint tracking and two for disturbance rejection are presented. Initially, the process is at the linearization point. The MPC is activated immediately after start up and tries to maintain the minimum purity and recovery values given, and at the same time, maximize productivity and minimize desorbent requirement.

It must be noted that the setpoint of F_{PD} must be kept large enough so that the controller can search a wide space for optimal points. Therefore, it is acceptable if F_{PD} cannot reach the setpoint given. It would suffice if the controller can just approach the offline optimization results.

For setpoint tracking (case 1), the setpoints are changed while other system parameters are kept constant. For disturbance rejection (case 2), the virtual plant is started up with a different set of Henry constants to investigate the effect of any change in the system that may alter the isotherm parameters. For the second case of disturbance rejection (case 3), a sudden change in feed concentration is applied during operation. In both cases the controller tries to maintain the process at its original setpoint. The summary of the case studies are given in Table 6.5. For disturbance rejection, the setpoints are chosen to be close to the linearization point. We also analyze the steady state offsets, which are by definition the difference between setpoints and final values. The final values are obtained by averaging the last five cycles.

Table 6.5: Summary of the case studies considered in this work. The order of setpoints is F_{PD} , P_A , P_B , Y_A , and Y_B . n_{ci} is the number of injection cycles.

Case	Description	Figure
1	Setpoints change from [0.6 95 95 90 90] to [0.6 98 98 95 95] at $n_{ci} = 99$	6.5, 6.6
2	Immediate change in H_A and H_B from [3.49 1.41] to [3.32 1.34]	6.7, 6.8
3	Change in feed concentration from 34.91 to 34.0 g/L at $n_{ci} = 38$	6.9, 6.10

6.5.1 Setpoint tracking

The output results for setpoint tracking are given in Figs. 6.5 and 6.6. The controller initially brings the purity and recovery values to the lower limits and in the mean time,

increases the performance function. This is in fact in agreement with what we observed in offline optimization earlier; as the constraints are relaxed, better performance is expected.

When the setpoint change is applied, the controller brings back the purity and recovery values to the higher points, which is very close to the optimal point obtained from the offline optimization analysis. This confirms the ability of the controller to regain the optimal points if operating parameters remain the same as of the offline optimization.

It must be born in mind that as the output variables are highly coupled in a nonlinear way, it may not be possible to exactly satisfy any arbitrary purity and recovery set values. Therefore, it would suffice if the controller can maintain the minimum required values given as the setpoints. On the other hand, the minor differences observed between the results of offline optimization and online optimizing control basically arise from the fact that two different optimization techniques are taken for these problems. The setpoints, final values, and respective offsets before and after changing the setpoints are given in Table 6.6.

Table 6.6: Setpoints, final values, and offsets (in percent) for setpoint tracking (case 1) before and after changing the setpoints.

	Before change				After change			
	P_A	P_B	Y_A	Y_B	P_A	P_B	Y_A	Y_B
Setpoint	95	95	90	90	98	98	95	95
Final value	95.2	95.6	90.6	91.8	97.8	97.8	95.1	95.05
Offset (%)	-0.2	-0.6	-0.6	-2.1	+0.1	+0.2	-0.1	-0.05

6.5.2 Disturbance rejection

In case 2, we investigate the effect of change in the adsorption properties on the closed-loop response. From the beginning of operation, the Henry constants are changed to lower values. This causes an initial drift in purity and recovery values as can be seen in Fig. 6.7, and then the controller quickly responds to this change by decreasing the injection volume. This is indeed reasonable as the lower Henry constants are closer to each other and this reduces the column efficiency. Therefore, lower sample amounts can be processed at the same resolution. Although the new steady state value of F_{PD} is lower than the original point of operation, it is clear from Fig. 6.8(a) that the controller can quickly recover F_{PD} after an undershoot. It is worthy of attention that the final improvement is in both productivity and desorbent requirement.

The initial response to the disturbance is slightly oscillatory, but the oscillations quickly diminish as the online state estimator updates the states based on the new plant information and besides, the controller brings back the process closer to its normal operating point. The setpoints, final values, and respective offsets are given in Table 6.7.

In case 3, the feed concentration is decreased after the process has reached steady state. The immediate effect is loss of purity of component A and recovery of component B. However, the controller takes immediate action to recover the setpoints. It first responds with decreasing injection volume and then it increases injection volume to optimize F_{PD} . The final steady state corresponds to a lower value of F_{PD} as can be seen in Fig. 6.10(a). Therefore, the decrease in feed concentration deteriorates

(a)

(b)

Figure 6.5: Output results of setpoint tracking (case 1); the setpoints of purity and recovery values are changed from [95 95 90 90] to [98 98 95 95] at 99th injection: (a) purities; (b) recoveries.

Table 6.7: Setpoints, final values, and offsets (in percent) for change in Henry constants (case 2).

	P_A	P_B	Y_A	Y_B
Setpoint	98	98	95	95
Final value	98.2	97.994	94.6	95.6
Offset (%)	-0.2	+0.006	+0.4	-0.6

Figure 6.6: Output results of setpoint tracking (case 1); the setpoints of purity and recovery values are changed from [95 95 90 90] to [98 98 95 95] at 99th injection: (a) performance function F_{PD} ; (b) productivity and desorbent requirement. Min/max values are obtained from offline optimization.

(a)

(b)

Figure 6.7: Output results of disturbance rejection (case 2); the Henry constants are changed from $[3.49 \ 1.41]$ to $[3.32 \ 1.34]$ immediately after startup: (a) purities; (b) recoveries.

Figure 6.8: Output results of disturbance rejection (case 2); the Henry constants are changed from [3.49 1.41] to [3.32 1.34] immediately after startup: (a) performance function F_{PD} ; (b) productivity and desorbent requirement. Min/max values are obtained from offline optimization.

the performance of the process. In this regard, the initial point was at least optimal compared to the final state. Actually, the offline optimization results indeed reaffirm this finding that at this fixed value of cycle time, no better point can be found at lower feed concentrations. The setpoints, final values, and respective offsets are given in Table 6.8.

Table 6.8: Setpoints, final values, and offsets (in percent) for disturbance rejection (case 3) before and after changing feed concentration.

	Before change				After change			
	P_A	P_B	Y_A	Y_B	P_A	P_B	Y_A	Y_B
Setpoint	98	98	95	95	98	98	95	95
Final value	97.9	97.8	95.1	95.1	97.7	97.9	95.3	94.7
Offset (%)	+0.1	+0.2	-0.1	-0.1	+0.3	+0.1	-0.3	+0.3

6.5.3 Analysis of inputs

Variations of inputs for the three case studies are given in Figs. 6.11-6.13. It is apparent that injection volume plays the major role in both setpoint tracking and disturbance rejection. However, desorbent flow rate only takes minor steps. In fact, as suggested by the results of offline optimization, desorbent flow rate and cycle time are coupled together for majority of optimal solution points. Once one of them is fixed, the other would also automatically be fixed. See Section 5.4.4 in Chapter 5 for further discussion in this regard. Three cut intervals also take minor steps, but in this case, it must be emphasized that the effect of cut intervals on purity/recovery values can be significant. In other words, they may have a large gain with respect to purity/recovery outputs.

6.6 Interim conclusion

In this work, we implemented a model predictive control scheme with the ultimate objective of maximizing profitability, while the constraints (i.e. product specifications and process limitations) are satisfied. The proposed MPC scheme relies on an empirical model for online state estimation and prediction. This contrasts other approaches in which a detailed model is utilized online or robust operation is guaranteed via offline calculations.

After investigating several models in various orders, we successfully fitted an ARX model to the dynamic behavior of the ISCC process on a ‘cycle to cycle’ basis. The model residuals are within acceptable ranges, showing that unmodeled dynamics are negligible. Although the ISCC process is highly nonlinear in terms of input-output relations, it has rather fast, simple dynamics, which can be explained by low-order models. This task was done once and for all in an offline manner.

One advantage of such small models is the ease of identification and online updating/estimation. The larger the empirical model is, the more the danger of overfitting the data is as well. Another advantage of simpler models is that in general, closed-loop response is faster, which is a great advantage for our case as the off-spec products are minimized during startup or change in setpoints.

(a)

(b)

Figure 6.9: Output results of disturbance rejection (case 3); feed concentration is changed from 34.91 to 34.0 at 38th injection: (a) purities; (b) recoveries.

Figure 6.10: Output results of disturbance rejection (case 3); feed concentration is changed from 34.91 to 34.0 at 38th injection: (a) performance function F_{PD} ; (b) productivity and desorbent requirement. Min/max values are obtained from offline optimization.

(a)

(b)

Figure 6.11: Manipulated variables for setpoint tracking (case 1): (a) injection volume and desorbent flow rate; (b) three cut intervals.

(a)

(b)

Figure 6.12: Manipulated variables for change in Henry constants (case 2): (a) injection volume and desorbent flow rate; (b) three cut intervals.

Figure 6.13: Manipulated variables for change in feed concentration (case 3): (a) injection volume and desorbent flow rate; (b) three cut intervals.

In this work, we used Kalman filtering for online state estimation though the final goal was to provide predicted outputs to the controller. We used the offline identified model as the basis. The model is internally converted to state space and then augmented with presumed noise and unmeasured disturbance models. The role of the state estimator is twofold: to reduce the measurement noise and minimize the error between measured and calculated outputs. The results suggest that the state estimator is quite effective for with minimal a priori information, it can capture the effects of disturbances.

The proposed ‘cycle to cycle’ MPC scheme was tested for setpoint tracking and disturbance rejection. When the process is digressed from its nominal operating point due to a setpoint change or under the effect of a disturbance, minor oscillations may occur. However, given sufficient time for state estimation, the Kalman filter is able to adapt to the new operating point and hence the oscillations disappear. The final states are very close to what we obtained from offline optimization studies, meaning that the controller can effectively find optimal points even when it operates far from its nominal operating point or in the presence of disturbances.

It was identified that injection volume has the major role in setpoint tracking and disturbance rejection, though fine tuning is done via adjusting four other inputs. In fact, three cut intervals can have important effects on the outputs, which are nonlinear and subject to the operating point. On the other hand, the controller tries to take only minor changes in desorbent flow rate.

It must be emphasized that the output parameters in particular purities and recoveries are highly coupled, and they may not be simultaneously fixed at a specific arbitrary setpoint. This is indeed similar to the limitations imposed on SMB because in that case, purities and recoveries are also related to each other [75]. These interrelations affect the performance of any controller that tries to control all of the above mentioned variables.

In many previous studies, recovery was not included as a constraint [18, 20, 22]. One reason is that usually recovery is directly related to productivity. Therefore, maximizing productivity necessitates maximizing recovery in many cases. This means that the setpoint on recovery must be inevitably relaxed. This explains the rather larger offsets observed on tracking recovery values. Nonetheless, a negative recovery offset (i.e., measured value greater than setpoint) is acceptable regarding fulfilling process constraints.

An important issue to note is that in contrast to offline optimization, the MPC output weight factors which are basically set to regulate the relative importance of outputs, cannot be freely increased here because there is always an upper bound on them imposed by the stability requirements of the controlling scheme. They also affect the closed-loop dynamics. In general, we tried to adjust them close to their upper bounds to obtain a fast and stable response.

Nomenclature

Dr	desorbent requirement [L/g]
d	plant pure time delay [-]
dt_{ci}	cut intervals [s]
F_{PD}	performance function [-]
H_i	Henry constant of species i [-]
$M(k)$	innovation gain matrix [-]
m	control horizon [-]
n_a	number of poles [-]
n_b	number of zeros [-]
n_{ci}	number of injection cycles [-]
n_k	number of plant pure time delays [-]
n_u	number of inputs [-]
n_y	number of outputs [-]
p	prediction horizon [-]
P	purity [%]
$P(k)$	error covariance matrix [-]
Pr	productivity [g/(min g)]
q	time-shift operator [-]
Q	volumetric flow rate [mL/min]
S_p	condition for peak detection [-]
S_v	condition for valley detection [-]
t_{cy}	cycle time [s]
$u(k)$	inputs [-]
V_j	equal concern for relaxation of j th constraint [-]
V_{inj}	injection volume [μ L]
$w_{i,j}$	weight factors in formulating the MPC cost function [-]
$x(k)$	model states [-]
$\hat{x}(k)$	estimated states [-]
$y(k)$	measured outputs [-]
$\hat{y}(k)$	estimated/simulated outputs [-]
y_{UV}	UV signal [mAU]
Y	recovery [%]

Greek letters

ϵ	slack variable [-]
λ	weight factor in performance function [-]
ρ_ϵ	weight factor of slack variable [-]

Subscripts and superscripts

A	more retained compound
B	less retained compound
D	desorbent
F	feed
inj	injection
j	jth element of array
min	minimum
max	maximum
s	steady state
sp	setpoint

Chapter 7

Conclusions and outlook

Preparative chromatography is a key processing method of separation and purification of variety of low-volume high-value products including proteins, pharmaceuticals, and general-purpose chemicals. In particular, it is also one of the few methods of production of enantiopure compounds.

Preparative chromatography is limited to the application of a solid phase, which has to be stationary for practical reasons. Therefore, many conventional separation schemes are impractical when applied to chromatography. Instead there are innovative methods, which have been developed over time to overcome process limitations in this field.

Stacked injection is a conventional method in this field, which is simpler and less capital intensive than SMB. However, its profitability is low. As we showed in this thesis, stacked injection operating procedure can be modified for better profitability. Besides, it has not been fully automated so far, which is also necessary for more efficient operation. We aimed at both aspects in this thesis.

The fraction-collection mechanism and online monitoring system are important parts of every automated preparative work. An efficient online monitoring system is still an open problem especially for the separation of chiral compounds. Therefore, we included the design of the monitoring system in conjunction with the fraction collector in our objectives.

It was apparent that extensive work had to be done on the simulation side because available numerical solutions for chromatography were either inaccurate or computationally expensive. There were interesting numerical methods recently proposed in the literature, but their application to chromatography was rare. From state of the art techniques, we implemented finite-volume based numerical methods which are stable, fast, and accurate and hence perfectly suitable for control and optimization studies. They were key elements in deploying efficient application of evolutionary optimization algorithms, which despite remarkable capabilities, would otherwise suffer from heavy computational burden. These paved the way for the implementation of a model predictive control scheme to ensure optimal operation even in the presence of disturbance or model uncertainties.

We conclude here that we were successful in improving the stacked injection process though we could not achieve the profitability of an equivalent SMB. Our monitoring system was successful for steady state runs and can be an important instrument in this line of work. The process is also equipped with a human-machine interface that is

capable of running the process and automatically carrying out injections and fraction collections at steady state runs. Simulation and theoretical studies were also of novelty and have received attention.

The important outcomes of this thesis are as follows:

Regarding process hardware, the standard components of commercial HPLC devices were modified to obtain better process performance and facilitate online monitoring. Instead of autosamplers, we utilized a simpler but faster mechanism. A pair of customized intermediate vials was also introduced in order to connect the online monitoring system to the process. Problems occurring because of air leakage during fraction collection and imperfect mixing were alleviated in this way. The system is both faster and less expensive compared to similar commercial devices.

A novel online monitoring system based on the application of two parallel customized HPLC units was introduced and realized. The proposed device can increase the sampling rate of ordinary online HPLC units with an acceptable level of accuracy. It can readily be used for both chiral and achiral compounds without any limitations. It is also robust to process variations such as pressure fluctuations, impurities, etc.

We realized the process and its online monitoring system in a semi-preparative scale. We also developed the human-machine interface (HMI) software on site for automation and monitoring. In particular, the HMI can handle automatic injection, peak detection, and fraction collection seamlessly. It is worthy of attention that injection and fraction collection appear as two asynchronous time-scheduling tasks. Each of them comprises of several time constraints, which must be satisfied together. This software can run the process in steady state mode without operator intervention. The operator can supervise the process from a ‘main menu’, which contains manipulating controls, plots of elution profiles, pressure levels, etc.

We investigated the main numerical methods for the simulation of chromatographic model equations in search for better speed, accuracy, and stability. Under the broad family of finite-volume schemes, TVD and WENO schemes were more promising. We finally concluded that van Leer flux limiter and third-order WENO scheme were competent for our applications. Later, we extensively used the WENO scheme as the backbone of simulation for large-scale optimization and online optimizing control.

Using genetic algorithm (GA), the multi-objective optimization of the ISCC process was carried out for the separation of guaifenesin enantiomers with the objectives of maximizing productivity and minimizing desorbent requirement, while fulfilling the product constraints (i.e., purity/recovery) and hardware limitations (e.g., maximum allowable pressure drop and minimum cycle time).

The results demonstrated that overlapped peaks (either from the same cycle or from adjacent cycles) can be admitted advantageously to enhance productivity and decrease desorbent requirement especially for lower purity/recovery requirements. We also compared ISCC and SMB in both ideal and non-ideal conditions and concluded that although ISCC can ideally be as efficient as SMB, it may not compete with SMB under non-ideal conditions.

It is worthy of attention that offline optimization alone cannot guarantee robust and optimal operation in the presence of any unmeasured disturbance or process uncertainty as the final solution is inevitably infeasible or suboptimal. Therefore, we implemented a ‘cycle to cycle’ model predictive control (MPC) scheme, which utilizes an identified model for the prediction of the process evolution. Results showed that

the MPC scheme not only can carry out setpoint tracking and disturbance rejection efficiently, it can also explore optimal solutions in the space defined by manipulated variables. This means robust optimality can be achieved with efficient implementation of MPC.

7.1 Outlook

As mentioned earlier, overlapped peaks can advantageously be used for reduced purity/recovery requirements. An interesting extension of this work could be recycling from both waste fractions similar to steady state recycling (SSR). We believe this modification can even boost the performance of the available SSR processes as currently only one fraction is recycled and no overlapping from adjacent cycles is allowed in these processes. However, this scheme would complicate the process design and operation. Regarding process design, obtaining analytical solutions for the case of overlapped peaks from adjacent cycles is not straightforward and this is a major problem to address in designing SRR processes. Regarding process dynamics, recycling may cause complex dynamic behavior, which must be carefully investigated for controller design.

The fraction-collection scheme can be used for other types of isotherms such as anti-Langmuir type. The order of waste and fraction-collection cut intervals can also be rearranged to improve flexibility. For example, for Langmuir isotherm, in some cases, it would be better if fraction collection starts from the second fraction, and the first fraction is considered as waste or rework.

Artificial neural networks (NN) have proved their remarkable capabilities for simulation/prediction of complex processes. Actually, we briefly investigated the application of recently developed dynamic neural-network facilities on MATLAB for our process. Results showed promising performance for simulation. However, one of the obstacles for further application of NN is that for MIMO processes, neural networks cannot be utilized for model predictive control using current MATLAB facilities.

Heavy computational effort for handling neural networks is also a drawback of these modeling facilities. Moreover, we must be aware of the overfitting pitfalls arising when complex models are supposed to be fitted with limited sampling data available in real-time applications. Therefore, the performance of linear models and neural networks must be juxtaposed in practice to draw the final conclusion.

We have not implemented the proposed MPC scheme in practice, which can be a direct extension of this work. Addition of cycle time as a manipulated variable to the controller scheme can also be a useful extension. Of course when offline optimization results are available, additional complexity of a variable cycle time may not justify this modification as one can roughly identify the optimal operating point in terms of decision variables beforehand. The effect of manipulating cycle time for small deviations from nominal operating point would be minor. It must be noted that for a variable cycle time, the process modeling must be revised. The linearization task will also be subtle because cycle time has a nonlinear effect. Moreover, the MPC optimization problem must be reformulated because in practice, cycle time can take only discrete values, which leads to mixed-integer programming.

With the strong tendency towards separation and purification of macromolecules such

as DNA and proteins, we see the potential of the ISCC process for the new applications. However, we must take into account the physical limitations they may impose on the process design and operation. For example, perfect mixing is essential in the intermediate vials, which is a function of the physical properties of both mobile phase and solute. Therefore, it might be necessary to enhance the mixing through better design or better operating conditions when large molecules are to be processed.

Triangle theory is a well known and well established method of analysis of SMB under ideal assumptions, which can help to predict the purity of products as well as the optimal operating conditions. The methods utilized in Chapter 4 for single-column chromatography can be extended to obtain similar expressions for this process, which can describe the complete separation region and optimal operating conditions in terms of a few dimensionless variables.

Extending the results of single-column chromatography to a multi-component separation must be straightforward at least in the framework of complete separation and recovery because we can simply divide the elution profile into any number of pure fractions as we ideally did for a binary system. However, for SMB, we need to add more effluents in addition to extract and raffinate or cascade multiple units. The underlying formulation and operation is more difficult.

Appendix A

List of Abbreviations

ARX	autoregressive with exogenous input model
CDS	central differencing scheme
CFL	Courant–Friedrichs–Lewy
CPU	central processing unit
CSP	chiral stationary phase
EA	evolutionary algorithm
ECR	equal concern for relaxation
EMG	exponentially modified Gaussian
ENO	essentially non-oscillatory
FD	finite difference
FE	finite element
FV	finite volume
GA	genetic algorithm
GRM	general rate model
HMI	human–machine interface
HPLC	high performance liquid chromatography
ISCC	improved single-column chromatography
IV	instrumental variable
LS	least squares
MCSGP	multi-column solvent gradient purification
MIMO	multi-input multi-output
MPC	model predictive control
NN	neural networks
NSGA	non-dominated sorting genetic algorithms
OCFE	orthogonal collocation on finite elements
ODE	ordinary differential equation
PDE	partial differential equation
PEM	prediction-error method
PFD	process flow diagram
PID	proportional–integral–derivative
QP	quadratic programming
RPM	rounds per minute
SCC	single-column chromatography
SISO	single-input single-output

SMB	simulated moving bed
SS	state space
SSR	steady state recycling
TMB	true moving bed
TVD	total variation diminishing
UDS	upwind differencing scheme
UV	ultraviolet
WENO	weighted essentially non-oscillatory

Appendix B

Homogeneous Formulation of Case Study A

It is possible to rewrite Eq. 3.9 as a homogeneous hyperbolic PDE by defining a new set of variables, G and g

$$\frac{\partial g}{\partial t} + \frac{\partial G}{\partial z} = 0 \quad (\text{A-1})$$

where

$$g = c + \frac{1-\varepsilon}{\varepsilon}n \quad (\text{A-2})$$

$$G = vc \quad (\text{A-3})$$

For linear and Langmuir isotherms, explicit expressions, relating c and g , can be obtained as shown below

For linear isotherm

$$c = \frac{g}{1 + \frac{1-\varepsilon}{\varepsilon}H} \quad (\text{A-4})$$

For Langmuir isotherm

$$c = \frac{1}{2K} \left(Kg - \left(\frac{1-\varepsilon}{\varepsilon}H + 1 \right) + \sqrt{\left(\frac{1-\varepsilon}{\varepsilon}H + 1 - Kg \right)^2 + 4Kg} \right) \quad (\text{A-5})$$

This formulation provides the same propagation speed as of the original equation for both smooth and discontinuous parts of the solution, eliminating the possibility of a wrong weak solution [99]. Based on this approach, the local propagation speed for smooth regions is

$$v_{cont} = \frac{\partial G}{\partial g} = \frac{v}{1 + \frac{1-\varepsilon}{\varepsilon}n'(c)} \quad (\text{A-6})$$

which can be used to calculate CFL number. And for the shock

$$v_{shock} = \frac{\Delta G}{\Delta g} = \frac{v}{1 + \frac{1-\varepsilon}{\varepsilon} \frac{\Delta n}{\Delta c}} \quad (\text{A-7})$$

This equation is used for obtaining shock fronts in the analytical solutions.

Although this approach is suitable for equilibrium theory, it cannot be readily extended to the detailed model where mass-transfer resistance is accounted for. Besides, the choice of the right functional form needs in-depth knowledge of the physics of the problem and may not be straightforward especially for nonlinear isotherms. Furthermore, by applying this approach, we have experienced more computational time without any improvement in the results. Therefore, we prefer to use the approach described in Section 3.6.5.

Appendix C

Maximal Local Propagation Speed

To calculate the maximal local propagation speed, we consider the following set of PDEs.

$$\frac{\partial g}{\partial t} + \frac{\partial G}{\partial z} = 0 \quad (\text{B-1})$$

$$\frac{\partial \rho}{\partial t} + \frac{\partial(v\rho)}{\partial z} = 0 \quad (\text{B-2})$$

where the first equation is the homogeneous formulation of the governing equation (Eq. 3.9), and the second equation is the continuity equation. ρ is the density of fluid.

The convective flux vector for this system is

$$\mathbf{f} = \begin{bmatrix} G \\ v\rho \end{bmatrix} = \begin{bmatrix} vc \\ v\rho \end{bmatrix} \quad (\text{B-3})$$

The Jacobian of $\mathbf{f}$ is

$$\mathbf{f}' = \begin{bmatrix} \frac{\partial G}{\partial g} & 0 \\ 0 & v \end{bmatrix} \quad (\text{B-4})$$

Substituting Eq. A-6, we obtain

$$\mathbf{f}' = \begin{bmatrix} \frac{v}{1 + \frac{1-\varepsilon}{\varepsilon} n'(c)} & 0 \\ 0 & v \end{bmatrix} \quad (\text{B-5})$$

The propagation speeds are absolute values of eigen values of this matrix. Looking at the eigen values of $\mathbf{f}'$, it is clear that in chromatography, the maximal local propagation speed is the linear velocity, v . Therefore

$$a_{j\pm 1/2} = v \quad (\text{B-6})$$

Appendix D

CFL Number

CFL number is defined as

$$CFL = \frac{a\Delta t}{\Delta z} \tag{C-1}$$

where a is the maximal local propagation speed, which in our case is the linear velocity, v . The size of Δt is regulated by variable step solver (in our case ode45) and therefore it varies along the time domain. The stability is guaranteed if the parameters of the ODE solver are set up properly. Nevertheless, if a CFL condition is given for the problem, a higher bound on Δt can be defined accordingly.

Although ode45 is in general an efficient ODE solver, we decreased the relative tolerance of integration from its default value (i.e., 10^{-3}) to 10^{-4} in order to obtain better results.

Appendix E

Process Flow Diagram (PFD)

Appendix F

Publications

Journal publications

- Kazi, M. K., B. Medi and M. Amanullah. Optimization of an improved single-column chromatographic process for the separation of enantiomers. *J. Chromatogr. A*, 1231:22-30, 2012.
- Medi, B. and M. Amanullah. Application of a finite-volume method in the simulation of chromatographic systems: Effects of flux limiters. *Ind. Eng. Chem. Res.*, 50(3): 1739-1748, 2011.
- Medi, B., M. K. Kazi, and M. Amanullah. Model predictive control of the improved single-column chromatographic separation process, In Preparation.
- Medi B., M. K. Kazi, and M. Amanullah. Improved single-column chromatographic separation process with recycling, In Preparation.
- Medi B., M. K. Kazi, and M. Amanullah. Nonlinear direct inverse method: a shortcut way for isotherm determination and calibration, In Preparation.

Conference proceedings

- Medi B. and M. Amanullah. Efficient numerical methods based on finite volume for handling steep fronts in chromatographic separation processes. In PBAST5, page 107, Singapore, 2009.

Poster presentations

- Medi B., M. K. Kazi, and M. Amanullah. Comparison of single-column chromatography and simulated moving bed process at optimal operating points. In AIChE Annual Meeting, page 630f, Minneapolis, USA, 2011.

Patent

- Medi B., M. K. Kazi, and M. Amanullah. Design of an improved single-column chromatographic separation process and its online monitoring system, filed on 6 March 2012 (patent pending).

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