

A Superstructure Approach for Optimization of Simulated Moving Bed (SMB) Chromatography

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ABSTRACT

One of the most successful continuous high-performance liquid chromatography (HPLC) processes for drug manufacturing is the Simulated Moving Bed (SMB). SMB is a multi-column, continuous, chromatographic process that can handle much higher throughputs than regular batch chromatographic processes. The process is initially transient, but eventually arrives at a cyclic steady state, which makes optimization very challenging, even more so when superstructure optimization is involved. To simplify the optimization problem, many researchers fixed the SMB structure, optimizing only the continuous variables, so they cannot be considered superstructure optimization. In this work, an SMB superstructure that can simultaneously optimize column structure and operation is proposed. The results showed that the superstructure proposed is reliable, and it is more efficient compared to current optimization approaches if the optimal column structure has to be identified.

Keywords: Modelling and Simulations, Process Design, Optimization, Particle Swarm Optimization, gProms, Superstructure, Simulated Moving Bed, Chromatography

INTRODUCTION

Chromatography is one of the most important separation processes in the pharmaceutical industry, used to purify valuable active pharmaceutical ingredients (APIs). The ability to efficiently extract pure (e.g., 99.9 wt%) APIs is crucial to ensure the health and safety of patients ingesting the medicine, but also to reduce waste and maximise profit. The most commonly used chromatographic process, high-performance liquid chromatography (HPLC), features a tightly packed stationary phase within a column, through which a mobile phase containing the feed mixture is passed. There are two operating modes for HPLC – batch or continuous. Although the continuous process is more complex in terms of design and operation, the pharmaceutical industry is slowly transitioning to adopting continuous processes as this mode can improve both efficiency and productivity.

The most successful continuous HPLC process for drug manufacturing is the Simulated Moving Bed (SMB). SMB is a multi-column, continuous, chromatographic process that can handle much higher throughputs than regular batch chromatographic processes. SMB usually

has four sections, the desorbent (D), extract (E), feed (F) and raffinate (R) sections, and simulates a counter-current flow between the stationary and mobile phases through periodical and synchronous switching of the inlet and outlet ports in the direction of fluid flow. Figure 1 illustrates the operating principle for an eight-column SMB (two columns per section, *aka* a 2222 SMB), where the ports move forward (in the direction of fluid flow) by one column after a switch time t_s , and finally return to the initial state after eight switches (i.e., after a complete cycle). The process is initially transient but eventually arrives at a cyclic steady state (CSS). Each SMB section can have a different number of columns, which must be determined carefully due to physical limitations (e.g., pressure drop) which may have a significant effect on the separation performance. These limitations pose challenges for the modelling and optimization of an SMB process, as will be briefly discussed below.

Firstly, consider the modelling of an SMB process. To capture both the transient startup stage and the CSS, the most straightforward method is to perform a dynamic simulation, where each cycle in the SMB process is simulated until the CSS is identified [1–3]. This approach is,

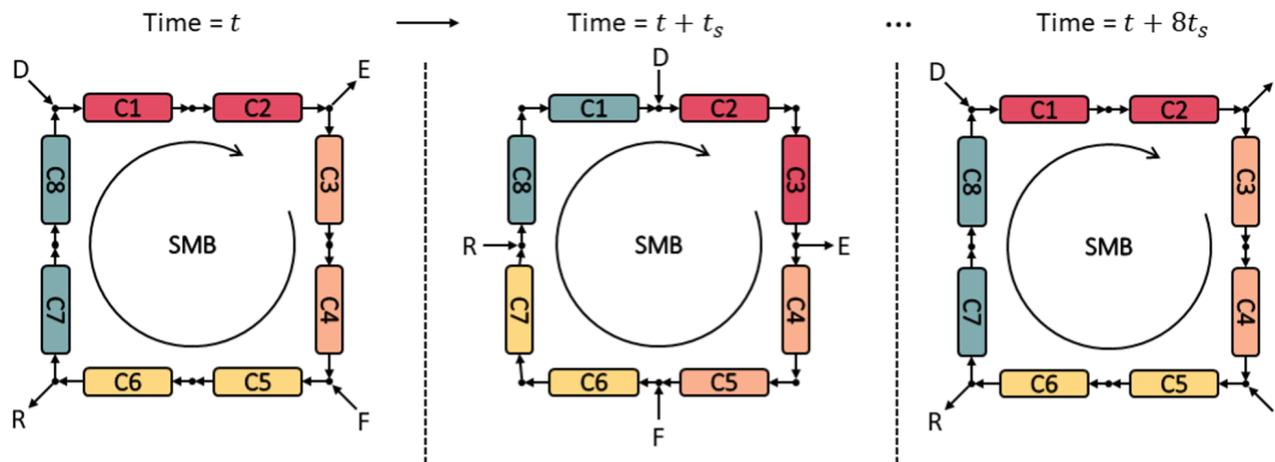


Figure 1. Operating procedure of an eight-column SMB (two columns per section), where t_s is the switch time, C_i is column i , and D, E, F, R are the desorbent, extract, feed, and raffinate flow rates, respectively. A complete cycle for this structure requires $8t_s$. The circular arrow represents the direction of fluid flow.

however, very time-consuming as CSS is often achieved only after a number of cycles. Information about the transient startup stage is usually redundant when considering optimization; as only the final CSS is of interest for SMB operation. By incorporating the CSS conditions as part of the optimization boundary conditions, the conditions at CSS can be simulated directly, making it faster than dynamic simulation for transient startup. There are two popular ways to include CSS conditions in the boundary conditions: (1) the method by Nilchan and Pantelides [4], where it is assumed that the conditions at the start and end of a cycle are identical, and (2) the method by Kloppenburg and Gilles [5], where the state variables at the outlet of a column are the same as that at the inlet of the next column. However, to incorporate CSS conditions as part of the boundary conditions, a fully discretized model (spatial and temporal domains discretized) is needed, which involves more equations and variables than the partially discretized model (only spatial domain discretized) used for dynamic simulation. It should be noted that the simulation time of both dynamic and direct CSS approaches are highly dependent on the grid discretization; finer grid provides more accurate separation behavior but greatly increases the simulation time, and vice versa. Therefore, whether the dynamic or direct CSS approach is more time-efficient will depend on the discretization grid and method used.

For optimization of SMB, most researchers have conveniently fixed the column structure and optimized only the continuous optimization variables (e.g., [3,6,7]). Only a few studies have considered SMB superstructure optimization, which allows identification also of the column design and arrangement. Kawajiri and Biegler [8–10] explored an SMB superstructure which took into account

the standard continuous variables as well as some structural configuration decisions (e.g., the number of columns in each section), but their superstructure was limited to a fixed total number of columns.

This work therefore aims to: (1) discuss and provide solutions for challenges related to handling the number of columns and switch actions in SMB superstructure modelling and optimization, and (2) propose a superstructure approach that allows for simultaneous optimization of the number of columns in each section, as well as the column dimensions (length and diameter) and the switching times and the flow rates. This superstructure optimization problem, which is a mixed integer non-linear programming (MINLP) problem, will determine not only the optimal configuration, but also simultaneously the column design as well as the operating procedure of the SMB process.

METHODOLOGY

This section will outline the key steps required to construct a superstructure model of an SMB process. Firstly, the superstructure flowsheet must be constructed. In most cases, models are solved with a numerical solver, meaning that the degrees of freedom must be carefully considered when constructing the model (e.g., the number of equations in *if* and *else* branches must be the same). This introduces challenges when handling optimization of the number of columns and port changes, and the solutions to these problems will be discussed. As previously mentioned, the model can be partially or fully discretized depending on the purpose of the study. This work will also discuss the conversion of a partially discretized model into a fully discretized model.

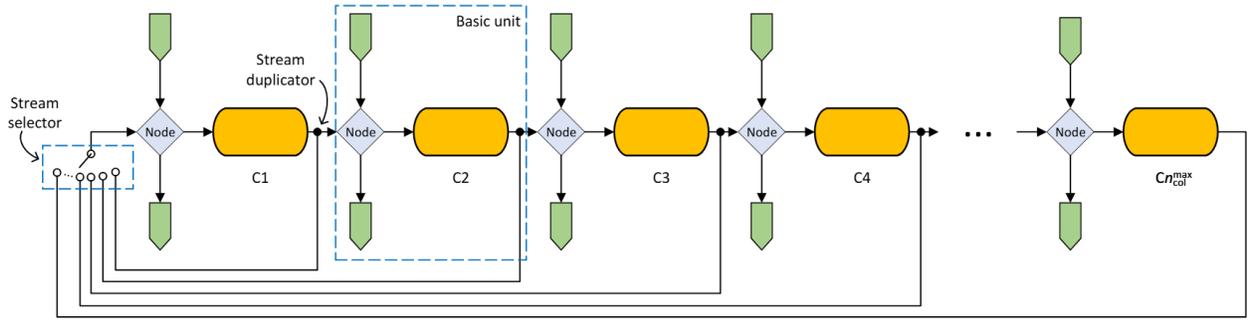


Figure 2. Flowsheet of the proposed SMB superstructure made up of n_{col}^{max} basic units (node + column).

Superstructure Flowsheet

The flowsheet of our SMB superstructure is shown in Figure 2. The basic unit is made up of two parts: (1) a node model, where it is modelled as an instantaneous mixer as proposed by Chan et al. [11], followed by (2) a chromatography column model consisting of a transport model (e.g., general rate model or equilibrium dispersive model) and an isotherm model (e.g., linear or Langmuir). The basic unit of node and column is then repeated n_{col}^{max} times, where n_{col}^{max} is the maximum total number of columns (not number of columns per section) considered in the optimization. This maximum number must be decided *a priori*. The outlet stream of each basic unit (i.e., outlet stream of the column), except for the last basic unit for which the outlet stream is a recycle stream, is connected to a stream duplicator. The stream duplicator does not physically exist, and its existence is solely to duplicate the outlet stream information: for the stream that is sent to the next basic unit (i.e., becomes the inlet stream to the node model) and for a stream selector used to identify the recycle stream location and therefore the optimal number of columns required. Only one stream selector is present in the flowsheet, and it is located prior to the first basic unit. The stream selector connects the recycle stream from the final column (i.e., the recycle stream from column n_{col}^{tot}) to the inlet of the first basic unit. The other recycle streams that are not selected are treated as redundant streams in the optimization.

Handle Number of Columns

As previously described, the SMB superstructure flowsheet consists of n_{col}^{max} basic units, and this is represented as an array of basic units in the model. When solving the model using numerical solvers, the number of equations cannot change during the simulation/optimization. Therefore, the size of the basic unit array must be fixed *a priori*. Since the number of columns in a section j , $n_{col,j}$, is an optimization variable, there are three possible cases: (1) $\sum_{j=1}^4 n_{col,j} > n_{col}^{max}$ which will be treated as an

infeasible simulation and discarded, (2) $\sum_{j=1}^4 n_{col,j} = n_{col}^{max}$ where no additional action is required, and (3) $\sum_{j=1}^4 n_{col,j} < n_{col}^{max}$ where there are “redundant” columns that need to be considered. Chia and Sorensen [12] discussed the handling of redundant membrane stages in a membrane superstructure, which is similar in principle to that of an SMB superstructure. Therefore, their strategy where all columns are simulated but the optimal result is collected from the optimal column n_{col}^{tot} will be used.

Handle Port Changes

Referring to Figure 1, a port is the black circle located before each column. For example, the desorbent stream is at port 1 at time t , at port 2 at time $t + t_s$, and at port 1 again at time $t + 8t_s$. There are four sections in a typical SMB, and each section has a port number allocated to it at any time. Therefore, a variable β_j (where j represents the four sections) is introduced to hold the information about the port number of each section at a given time. During SMB operation, a port moves forward by one column after a switch time t_s ; hence, the port number should increase by 1 after t_s . This change can be captured with an intermediate variable β_j^{raw} :

$$\frac{d\beta_j^{raw}}{dt} = \frac{1}{t_s} \quad \forall j \in \{1,2,3,4\} \text{ or } \{D,E,F,R\} \quad (1)$$

However, Equation 1 will increase the port number beyond the actual total number of columns n_{col}^{tot} . So, to limit the port number in the range $[1, n_{col}^{tot}]$, a modulo operator where $a \bmod b \equiv a - b \times \lfloor \frac{a}{b} \rfloor$ is applied:

$$\beta_j = [(\beta_j^{raw} - 1) \bmod n_{col}^{tot}] + 1 \quad \forall j \in \{1,2,3,4\} \text{ or } \{D,E,F,R\} \quad (2)$$

With Equation 2, the port number of each section at a given time can be identified, and further actions, such as determining the inlet flow rate of a node at a given time, can be performed using *if-else* statements.

Discretization of the Superstructure Model

The partially discretized superstructure model,

discretized in the axial direction of the column, has now been constructed. To transform this partially discretized model into a fully discretized model, firstly, all time-variant variables in the partially discretized model must have an additional temporal domain. Then, the initial conditions of the partially discretized model become the boundary conditions for the temporal domain in the fully discretized model. As discussed in the introduction, when formulating the boundary conditions, the CSS condition can be considered as repeating within a cycle [4] or matching inlet-outlet states between columns in a switch [5]. Both options are possible, but the latter allows faster simulation time as it involves fewer equations, hence is applied in this work. To complete the transformation into a fully discretized model, the time-derivative equations must also be transformed into partial derivative equations (e.g., $d\beta_j^{\text{raw}}/dt$ becomes $\partial\beta_j^{\text{raw}}/\partial t$).

Completing the steps above will yield a fully discretized model. The switch time t_s now becomes the upper bound of the temporal domain (i.e., becomes a parameter) and therefore cannot be optimized. To solve this issue, the temporal domain must be normalized. This can be done by introducing a new variable τ , so that $\tau = t/t_s$. This will also transform the range of the temporal domain from $t \in [0, t_s]$ to $\tau \in [0, 1]$. Finally, the partial derivatives need to be transformed with the following equation:

$$\frac{\partial}{\partial t} = \frac{\partial}{\partial(\tau t_s)} = \frac{1}{t_s} \frac{\partial}{\partial \tau} \quad (3)$$

After the transformation, the partial derivatives are expressed in terms of τ and not t . Therefore, t_s is freed from the boundary, and returns to becoming a variable that can be optimized (i.e., no longer a parameter).

MODEL COMPARISON

To demonstrate the performance of the proposed SMB superstructure model, the SMB equations and case study used by Dünnebier et al. [1] is considered. Since this work introduces both partially and fully discretized superstructure models, both models will be considered and compared.

Dünnebier et al. [1] developed a four-zone SMB with two columns in each zone, resulting in a 2222 SMB configuration. The detailed information, including equations of the distributed plug flow and the node, linear isotherm, node equations, and other necessary equations and parameter values, can be found in the literature [1,11], and will therefore not be presented in this work. The maximum allowed number of columns in the superstructure model is set as 12, however, in the optimization only 8 columns will be considered, i.e., 4 columns are “bypassed”. This is done to test the methodology and to demonstrate that the redundant 4 columns are not considered in the optimal solution.

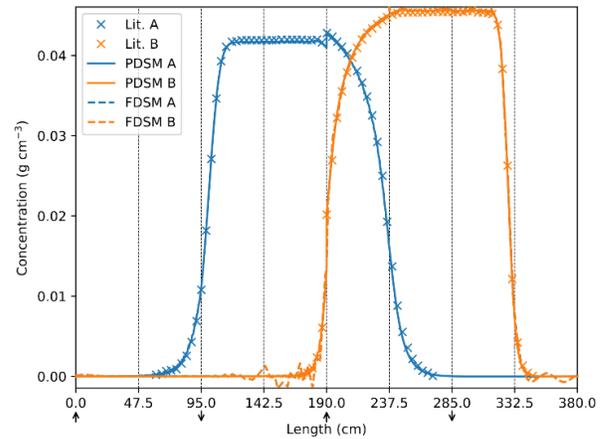


Figure 3. Comparison between the steady-state concentration profiles for components A (blue) and B (orange) obtained from literature (Lit.) [1], partially discretized superstructure model (PDSM), and fully discretized superstructure model (FDSM) at the end of a switching time.

The superstructure model in this work is developed in gPROMS. The partially discretized model contains only the spatial domain (i.e., discretization only along the column). A fourth-order orthogonal collocation finite element method (OCFEM) is chosen with ten collocation points. The fully discretized model involves an additional temporal domain. Both spatial and temporal domains in the fully discretized model are described using the fourth-order OCFEM as it can provide a sufficient accuracy with a reasonable computational time (trade-off not shown). All simulations and optimizations are performed on a workstation with a dual Intel Xeon Gold 6226R CPU (64 processors).

The steady-state concentration profiles along a single column for both components A (fructose) and B (glucose) are plotted in Figure 3. Overall, the simulation results from the proposed partially discretized and fully discretized superstructure models are very similar to those from literature. Figure 3 showed only the results for the first eight columns although the superstructure model is set to have 12 columns; the last four columns are bypassed so their results are ignored. The superimposing chromatograms also indicated that the bypassed columns do not affect the optimal results, so the methodology for handling number of columns can be used in optimization. It is noted that some oscillations due to numerical integration appears with the fully discretized model. This could be improved and minimized by using a finer discretization or choosing a more suitable discretization method. In terms of the purity of the products, the difference between the two proposed models is in the order of magnitude of 10^{-4} g g^{-1} , which is reasonable and more than sufficient for most optimizations. In terms of CPU

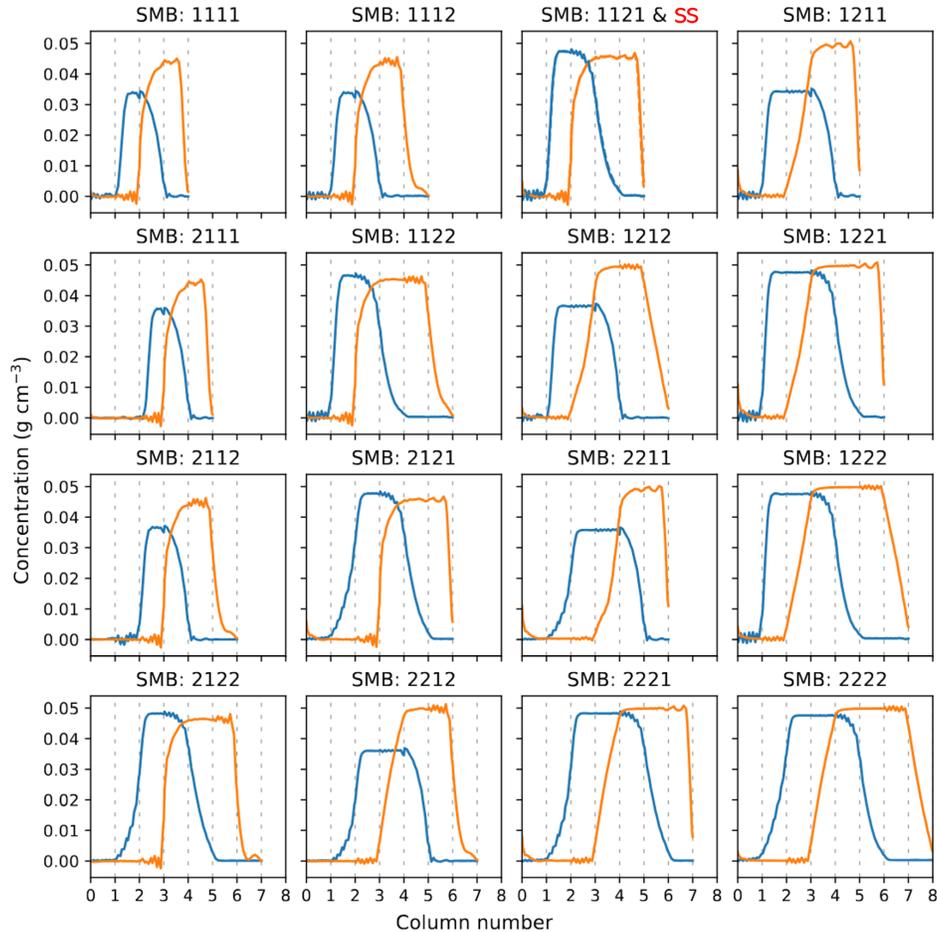


Figure 4. Concentration profiles along the columns for the simulated moving bed (SMB) structures investigated, including the optimal design obtained from individual optimization with fixed configuration and superstructure optimization (SS). The numbers in the title indicate the number of columns in the desorbent, extract, feed, and raffinate sections, respectively.

time, the fully discretized model is much faster, with about 8 s per simulation, while the partially discretized model requires 131 s per simulation. This significant difference makes the fully discretized model superior for optimization and cases requiring many simulations (e.g., for global sensitivity analysis).

SMB OPTIMIZATION

In the following, we will consider superstructure optimization where we simultaneously optimized the number of columns per SMB section, the design of the column (length and diameter) as well as the switch time and flow rates. The model, mixture, and other key parameter values are the same as previously.

In the following, the SMB configurations considered will have one or two columns in each section, which are considered as optimization variables, leading to 16 unique configurations as the maximum number of

columns is assumed to be 8 columns (e.g. 1111, 1112, 1122, etc). In addition, switch time (500 s to 900 s) and four volumetric flow rates ($0.01 \text{ cm}^3 \text{ s}^{-1}$ to $0.15 \text{ cm}^3 \text{ s}^{-1}$) are also optimized, leading to nine optimization variables in total (the number of columns for each of the four sections, the switch time and the four flow rates). The objective function considered is to maximize process efficiency defined by the following expression:

$$\text{efficiency} = \frac{\text{throughput}}{\text{rate of solvent consumption} \times \text{total col. volume}}$$

Two constraints are also taken into account: (1) outlet streams should be at least 99 wt% pure, and (2) the pressure drop within each column must be between 13 bar and 100 bar [11]. In terms of the optimizer, particle swarm optimization (PSO) is used due to its robustness and ability to jump out of a local optimum. Fifty particles are used in each iteration, and two stopping criteria are applied: (1) 200 maximum iterations, or (2) the best

objective values remain constant for 20 consecutive iterations, whichever satisfied first.

All concentration profiles for components A and B are plotted in Figure 4, for both individual configurations (i.e., optimization for a fixed column configuration) and for superstructure optimization (SS). Due to the limited space, the optimal designs and objective values for all configurations are not provided. The individual optimization results show that the best configuration is 1121 (i.e., only the feed section has two columns), with an efficiency of 1.086 mg cm^{-3} . There is a slight deviation between the individual optimal design for the 1121 configuration and the solution obtained via the superstructure methodology (1.086 vs 1.069 mg cm^{-3}) and this is due to local optimality. Note that the concentrations profiles are nevertheless identical in the figure.

CONCLUSION

This work proposed a novel SMB superstructure, which allows for simultaneous optimization of the number of columns in each SMB section together with other key design variables including column design and operating variables. The modification of the superstructure from a partially discretized model to a fully discretized model was demonstrated and tested, indicating good robustness. The superstructure model was considered to compare superstructure optimization with individual optimization of a fixed column configuration. Both approaches yielded the same optimal result, indicating good efficiency and reliability of the proposed superstructure. The superstructure allows for the direct determination of the optimal process, thus avoiding optimization for each possible column configuration. The proposed superstructure is versatile and can be applied to any type of mass transport model or isotherm used to describe the chromatographic system.

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