Process Robustness Evaluation for Various Operating Configurations of Simulated Moving Bed Chromatography

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Abstract

Simulated Moving Bed (SMB) chromatography is widely used in industry as a continuous separation technique. While various operating configurations have been proposed in the past, there has been a lack of attempts to evaluate the robustness of these configurations against uncertainties such as model inaccuracies and flow rate discrepancies. In this study, we quantify the uncertainty of product purity as posterior predictive distributions. In particular, the following three configurations are considered: the conventional SMB, 3-Zone SMB, and F-shaped SMB. It was found that the F-shaped SMB was the most robust configuration concerning the purity of two products, extract and raffinate.

**Keywords**: Robust Design; Uncertainty Quantification; Preparative Chromatography; Simulated Moving Bed

* 1. Introduction

Simulated Moving Bed (SMB) chromatography is widely employed as a continuous separation technique. This technique has been used for applications in many different industries such as petrochemicals, sugars, and pharmaceuticals. Figure 1(a) illustrates the schematic diagram of the conventional SMB (hereafter referred to as CSMB), which consists of four chromatographic columns. As can be seen in this figure, desorbent and feed are injected, while extract and raffinate are withdrawn simultaneously. After a certain period of time (step time), the SMB process switches the inlet and outlet ports simultaneously in the clockwise direction. This switching mimics the counter-current operation between the liquid and solid phases. In addition to CSMB, various operating configurations have been proposed for SMB processes. For example, Figure 1(b) represents the 3-Zone SMB (hereafter referred to as 3-Zone), and Figure 1(c) represents the F-shaped SMB (hereafter referred to as F-shaped), as reported by Kawajiri and Biegler (2008). Unlike CSMB, these two operating configurations do not involve a recycle stream.

The robustness of various operating configurations in the SMB process is of utmost importance and should be carefully evaluated. During the actual operation of the SMB process, it is often observed that the desired purity and recovery are not achieved due to various uncertainties, such as systematic bias of pump flow rates and observation errors. Therefore, the robustness of the SMB process, which quantifies the deviations from the desired purity, is a critical metric, particularly in industries that demand severe purity requirements, for instance, pharmaceuticals. However, few comparative assessments of robustness across different operating configurations have been addressed (Mota et al., 2007), while other performance metrics such as productivity and desorbent consumption have been investigated.

In this study, we quantify the uncertainty of purity as posterior predictive distributions to evaluate the robustness of the three operating configurations. We compare the uncertainty in purity for the three operating configurations: CSMB, 3-Zone, and F-shaped. In this comparison, a binary separation problem is considered using four chromatographic columns. This research considers four major uncertainties: flow rate discrepancies by pumps, feed concentration errors, uncertainties in model parameters (model errors)(Suzuki et al., 2021), and observation errors. Using the posterior predictive distributions, we evaluate the uncertainty in model predictions for these four uncertainties.



**Figure 1.** Schematic diagrams of (a) Conventional SMB, (b) 3-zone SMB, and (c) F-shaped SMB.

* 1. Methods
		1. Mathematical Modeling of SMB

In this study, the kinetic model is employed as the governing equation for the internal dynamics of SMB columns. Detailed information on the kinetic model can be found in Grosfils et al. (2007). This model is represented by the following two partial differential equations:

|  |  |
| --- | --- |
|  | (1) |
|  | (2) |

In the above equations, and represent the liquid and solid phase concentrations of component within the th column, respectively; and denote spatial and temporal coordinates, respectively; refers to the porosity; represents the internal flow rate in the th column; stands for the mass transfer coefficient; signifies the Henry’s constant, and denotes the affinity coefficient. Note that a competitive Langmuir adsorption isotherm, which is a nonlinear isotherm model, is adopted in Eq. (2). As illustrated in Figure 1, there exist four independent flow rates in SMB: desorbent , extract , feed , and raffinate . Details about the flow balances between columns can be found in Kawajiri and Biegler (2008). In this study, model parameters and operating parameters are defined in the following vector forms: and , where and are the feed concentrations for the two components.

The purity of the two products, extract and raffinate, is obtained from the average product concentrations when the SMB process reaches a cyclic steady state (CSS). The SMB process reaches CSS under sufficient operating time. The product concentration is an average concentration of extract () and raffinate () for each component under CSS. These four product concentrations are represented as the average product concentration vector , where . The purity of each product , where , is obtained from .

* + 1. Posterior Predictive Distribution of Product Purity

A statistical model accounting for observation errors in SMB experiments is formulated using the average product concentration and the parameter . In practice, is determined using analytical devices, for example, HPLC. These analytical measurements always contain observation errors. Assuming that the observation errors follow a Gaussian distribution, the observation (realization) can be expressed as:

|  |  |
| --- | --- |
|  | (3) |

where represents a set of parameters that have uncertainty in this study, and . It is assumed that and are independent of each other. is a deterministic model with as input and as output, i.e., . Here, is the measurement error vector. It is assumed that each component of follows an independent and identically distributed normal distribution . Based on Eq. (3), the realization through the statistical model are defined as follows:

|  |  |
| --- | --- |
|  | (4) |

The posterior predictive distribution is obtained by marginalizing the statistical model with respect to the posterior distribution of the parameters:

|  |  |
| --- | --- |
|  | (5) |

where, represents the posterior distribution of , i.e., the uncertainty obtained from the data. Here, since and are independent, the posterior distribution , which is model parameter uncertainty, can be expressed as the product of the multivariate probability density functions for and as: . Here, is the posterior distribution of which is obtained by Bayes' theorem (Yamamoto et al., 2021). In this study, operating parameter uncertainty is assumed as a multivariate probability distribution based on our experimental knowledge.

The probability of obtaining a product where the purity is at most , , is defined using a cumulative distribution function (CDF) as follows:

|  |  |
| --- | --- |
|  | (6) |

where is a predictive distribution of purity that is marginalized over the purity of product using Eq. (5). Note that equals 1 at . Using this , the probability that purity is greater than , , is defined as follows:

|  |  |
| --- | --- |
|  | (7) |

* + 1. Optimization of SMB Operations

To ensure a fair comparison for the three configurations, CSMB, 3-Zone, and F-shaped, the same optimization problem is solved for each operating configuration. Our optimization problem aims to maximize throughput as the objective, with four internal flow rates and the step time as decision variables. Inequality constraints are applied to the internal flow rates, specifying upper and lower bounds. Additionally, inequality constraints are imposed to set lower bounds on the purity of the two products, extract and raffinate. The optimization techniques are described in detail elsewhere (Kawajiri and Biegler, 2008).

* 1. Results
		1. Posterior Distribution and Optimal Operations

The posterior distribution was estimated by Sequential Monte Carlo (SMC) (Yamamoto et al., 2021). The left side of Table 1 displays the median and 95% credible intervals for the marginal posterior distribution of each parameter in . Here, was estimated using SMC with computer-generated batch experimental data that injects a small amount of feed into a single column which is used in the system of SMB (Suzuki et al., (2021)). The true values of the model parameters were adopted from Grosfils et al., (2007).

**Table 1.** Details of the model parameter uncertainty and the operating parameter uncertainty .

|  |  |
| --- | --- |
| Model parameter uncertainty | Operating parameter uncertainty |
| Parameter | Median with 95% CI(A) | Parameter | Mean | SD(B) |
|  |  | (C) |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  | 1.20 |  |
|  |  |  | 1.20 |  |

1. 95% credible interval; (B) standard deviation; (C) does not have uncertainty in operating configurations other than CSMB, where there is no recycle flow.

The operating condition of the three operating configurations was found by the optimization where the target purity was 98%. The lower bound for the purity constraint for both extract and raffinate was set at 99.0% in which a safety margin of 1% was added to the target purity of 98%. The upper and lower limits for internal flow rate were set at 4.0 m/h and 0.1 m/h, respectively. The model parameters were assumed to be at the median of the posterior distribution, .

We assumed as a multivariate normal distribution, where random variables are independent of each other, as discussed in Section 2.2. The mean and standard deviation of each random variable in operating parameter uncertainty are shown in Table 1. The mean values of the probability density functions for flow rates were the optimal solutions for each operating configuration. The standard deviation was set to 0.5% of the upper limit of the internal flow rate, 4.0 m/h. For the probability density functions of feed concentrations, the mean values were taken from the feed concentrations assumed in the optimization, [vol%] for , and the standard deviation was set to 1.25% of the mean. The observation error, in Eq. (3), was assumed to have a mean of zero and standard deviation of vol%.

* + 1. Posterior Predictive Distribution

The posterior predictive distributions of purity for the three operating configurations under the given uncertainties in Table 1 were estimated using the Monte Carlo method. In the Monte Carlo method, 10,000 sets of parameters were sampled from , and dynamic simulations of SMB were carried out until the process reached CSS each time, which was repeated 10,000 times. Additionally, 1,000 observation errors, , were sampled from and added to the 10,000 simulations. As a result, was approximated with 10,000,000 samples. The joint posterior predictive distribution of purity was obtained from the resulting .

 **Figure 2.** Marginal posterior distribution of raffinate purity (a) and extract purity (b) and cumulative distribution function of raffinate purity (c) and extract purity (d) for the three configurations: CSMB, 3-Zone, and F-shaped.

The robustness of raffinate purity is the highest in F-shaped, but differences among the three configurations are small. Figure 2 (a) and (c) show the marginal posterior predictive distributions and the CDFs, respectively, for raffinate purity of CSMB, 3-Zone, and F-shaped. The values of for raffinate purity are 0.620, 0.617, and 0.675 for CSMB, 3-Zone, and F-shaped, respectively, where notable differences cannot be seen.

Regarding extract purity, on the other hand, F-shaped demonstrates substantially higher robustness than the other two configurations. Figure 2 (b) and (d) show the marginal posterior predictive distributions and the CDFs of extract purity for the three configurations. The probability of obtaining purity values of 98.0% or higher, given by in Eq. (6), for CSMB, 3-Zone, and F-shaped yields values of 0.546, 0.899, and 0.970, respectively, where the highest value is achieved by F-shaped.

* 1. Conclusions

In this study, we quantified the robustness of three operating configurations: Conventional SMB, 3-Zone, and F-shaped. By comparing the posterior predictive distributions, we found that the robustness varies among the operating configurations under the same uncertainty. Regarding the purity of extract and raffinate, F-shaped demonstrated the highest robustness among the three operating configurations. This result implies that the robustness of purity can be highly influenced by operating configuration.

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