

# Sensitivity Analysis of Amino Acids in Simulated Moving Bed Chromatography

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**Abstract** We conducted a sensitivity analysis of the simulated moving bed (SMB) chromatography with the case model of the separation of two amino acids phenylalanine and tryptophan. We consider a four-zone SMB chromatography where the triangle theory is used to determine the operating conditions. Competitive Langmuir isotherm model was used to determine the adsorption isotherm. The finite difference method is used to solve nonlinear partial differential equation (PDE) systems numerically. We examined the effects of alterations in the operating conditions (feed-extract, feed-rafinate, eluent-extract, eluent-rafinate, recycle, and switching time) and the adsorption isotherm parameters (Langmuir isotherm parameters  $a$  and  $b$ ) on SMB efficiency. The variation range of operating conditions and Langmuir isotherm  $a$  was between -50 and 50% of original value and the variation range of the Langmuir isotherm  $b$  was between  $2.25^{-5}$  and  $2.25^5$  times of original value.

**Keywords:** sensitivity analysis, phenylalanine, tryptophan, SMB

## INTRODUCTION

Simulated moving bed (SMB) chromatography is a highly efficient form of continuous chromatographic process with high purity and yield and the added benefit of lowered mobile phase consumption. It is commonly employed for large-scale separation in petrochemical applications, sugar industries, and fine chemical industries for separation of amino acids and chiral compounds. Nevertheless, SMB chromatography is comparatively costly and complex to operate [1-3].

In the design of complex SMB chromatography, the optimization of the operation conditions relies on the determination of accurate adsorption isotherms. The success of experiments and modeling are directly related to accurate adsorption isotherms and their parameters. Most SMB chromatography is carried out under nonlinear conditions, and the nonlinear behavior should be considered properly in the nonlinear equilibrium isotherms. Langmuir adsorption isotherm is the most wide-used equilibrium isotherm among the various nonlinear isotherm models [4-6]. In many cases, adsorption isotherm parameters are determined by batch chromatography experiments. These parameters are subsequently used in the design and the simulation of SMB chromatography. However, the adsorption isotherm parameters of the batch chromatography are low in accuracy when applied to SMB chromatography processes. SMB chromatogra-

phy is operated under overloaded sample loading condition but a batch chromatography is operated under lower loading condition than SMB chromatography. These different loading conditions are occurred by the disagreement of the adsorption isotherm parameters in SMB chromatography. The other difficulty is the SMB operation. Because SMB chromatography is continuous process, it demands constant monitoring and maintenance of the flow rates and valve switching during its operation. Any disturbance has direct effects on the zone flow rate and the solid/liquid flow rate ratio resulting in reduced purity and yield of products.

The objective of this work was to establish the sensitivity of SMB process separating phenylalanine (Phe) and tryptophan (Trp) to changes in the isotherm parameters and the operating parameters [4].

## THEORY

The equilibrium-dispersion model is used as a material balance. The following PDE is the material balance for a chromatographic column [7].

$$\varepsilon_T \frac{\partial c_i}{\partial t} + (1 - \varepsilon_T) \frac{\partial q_i}{\partial t} + u \frac{\partial c_i}{\partial z} = \varepsilon_1 D_i \frac{\partial^2 c_i}{\partial z^2} \quad (1)$$

where  $c_i$  is the mobile phase concentration of component  $i$ ,  $q_i$  is the adsorbed solid phase concentration of component  $i$ ,  $\varepsilon_T$  is the total void fraction,  $\varepsilon_1$  is the interparticle void fraction,  $u$  is the superficial velocity of the mobile phase, and  $D_i$  is the axial dispersion coefficient of com-

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ponent  $i$ . A competitive Langmuir isotherm is used as the equilibrium adsorption isotherm model according to

$$q_i = \frac{a_i c_i}{1 + \sum_j b_j c_j} \quad (2)$$

where  $a_i$  and  $b_i$  are the Langmuir isotherm parameters.

PDE equations were calculated by the finite-difference method (FDM) and the steepest descent method. All simulation was done on a Pentium™ 4 personal computer. The following equations are the FDM formulas.

$$S\Delta z(\varepsilon_T c_i^{t+1,z} + (1-\varepsilon_T)q_i^{t+1,z}) = S\Delta z(\varepsilon_T c_i^{t,z} + (1-\varepsilon_T)q_i^{t,z}) + M_{10} + M_D \quad (3-1)$$

$$M_{10} = Q\Delta t(c_i^{t,z-1} - c_i^{t,z}) \quad (3-2)$$

$$M_D = \varepsilon_i D_i S \Delta t \left( \frac{c_i^{t,z+1} - c_i^{t,z}}{\Delta z} - \frac{c_i^{t,z} - c_i^{t,z-1}}{\Delta z} \right) \quad (3-3)$$

where  $S$  is the cross-sectional area of the column, and  $Q$  is the volumetric flow rate of the mobile phase. We can find  $q_i^{t,z}$  from Eq. 2 with the Steepest Descent Method.

The operation of SMB chromatography depends on the flow rates of four zones, as well as the switching time. Morbidelli *et al.* proposed the triangle theory, which is based on the equilibrium model [8]. Triangle theory disregards the axial dispersion and the mass transfer resistance. The parameter  $m_j$  is the flow rate ratio defined as the ratio of the net fluid flow rate versus the solid phase flow rate in zone  $j$ . Based on the flow ratio,  $m_j$ , the experimental conditions for the SMB were determined by

$$m_j = \frac{Q_j^{SMB} t^* - V \varepsilon_T}{V(1 - \varepsilon_T)} \quad (4)$$

where  $Q_j^{SMB}$  is the internal volumetric flow rate in zone  $j$ ,  $t^*$  is the switching time and  $V$  is the volume of a single column.

To achieve complete separation, the lower bound on  $m_1$  and the upper bound on  $m_4$  were kept explicit. However, the former does not depend on the other flow rate ratios, whereas the latter is an explicit function of the flow rate ratios  $m_2$  and  $m_3$ .

$$m_{1,\min} < m_1 < \infty \quad (5)$$

$$m_{2,\min}(m_2, m_3) < m_2 < m_3 < m_{3,\max}(m_2, m_3) \quad (6)$$

$$\frac{-\varepsilon_p}{1 - \varepsilon_p} < m_4 < m_{4,\max}(m_2, m_3) \quad (7)$$

where  $\varepsilon_p$  is the intraparticle void fraction of the column.

## RESULTS AND DISCUSSION

All simulation parameters and system parameters were either described in an earlier publication [4] or are as shown in Table 1. Isotherm parameters (Langmuir isotherm parameter  $a$  and  $b$ ) and operating conditions (*i.e.*, feed, eluent, extract, and raffinate flow, as well as the switching time) were variable parameters. The range of the variable parameters except the Langmuir isotherm parameter  $b$  was within 50 to 150% of the original values, and SMB system was simulated at regular intervals of 10%. The range of the Langmuir isotherm parameter  $b$  was within 2.25<sup>-5</sup> to 2.25<sup>5</sup> times of original value, and SMB system was simulated at regular ratios of 2.25 times. Because the arithmetic progression of the Langmuir isotherm  $b$  cannot have a significant effect on the SMB simulation result. Table 2 shows the range and intervals of the variable parameters used in the SMB simulation. Standard condition (Table 2) is highlighted in the triangle zone (Fig. 1) with a 20% safety margin. For variations of the feed-extract, the zone II flow rate was changed, the zone III flow rate was changed for the feed-raffinate variations, the zone I flow rate was changed for the eluent-extract variations, and the zone I, zone II, and zone III flow rates were changed for the eluent-raffinate variations.

Fig. 2 shows the changes of purity and yield of products for alterations in the feed-extract, feed-raffinate, eluent-extract, eluent-raffinate, recycle, and switching time. When the flow rates of the feed and extract stream were decreased, the zone II flow rate increased. For the opposite case, the zone II flow rate was decreased. The lowered zone II flow rate resulted in phenylalanine (Phe), the less retained sample, contamination of the extract stream translating into a reduction in tryptophan (Trp) purity and Phe yield. Fig. 2A shows that the purity of Trp and the yield of Phe were lowered for slow zone II flow rates (high feed flow rate). Because slow flow rates of zone II reduced the selectivity of the extract stream, its purity and the yield of the raffinate stream were also decreased. Fig. 2B shows that the purity of Phe and the yield of Trp also decreased when zone III had a high flow rate (high feed flow rate). Because high flow rate of zone III resulted in a reduction of the selectivity of raffinate stream, the purity of raffinate stream and the yield of extract stream were concomitantly lowered. Fig. 2C shows that the purity of Phe and the yield of Trp were also decreased when the zone I flow rate was too low (low eluent flow rate). Zone I is a key factor in the regeneration of the column. A low flow rate in zone I prohibited regeneration of the column in the given switching time causing contamination by the extract material (*i.e.*, Trp) which moved to zone III or IV during the following switching times. The extract material (Trp) was thus mixed with the raffinate material (Phe) in the raffinate stream. In the following three simulations (the eluent-raffinate, the recycle, and the switching time), three or

**Table 1.** System and simulation parameters

System parameters		Simulation parameters	
Column length (cm)	21.70	Run cycles	4
Column internal diameter (cm)	2.50	Total switching count	32
Interparticle void fraction	0.30	Axial dispersion coefficient (cm/min)	
Intraparticle void fraction	0.55	Phenylalanine	0.0353
		Tryptophan	0.0353

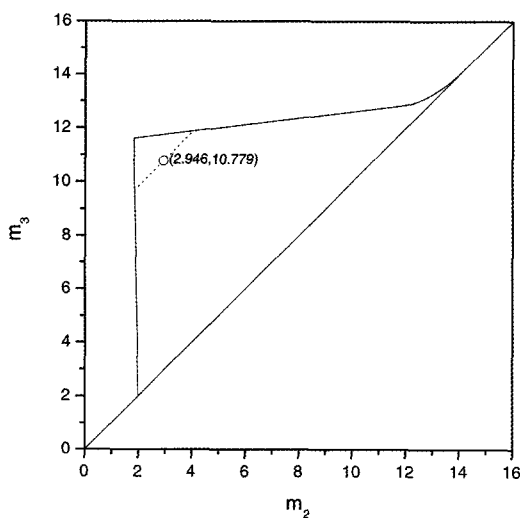
**Table 2.** The variable parameters used in SMB simulation

Feed – Extract		Feed – Raffinate		Eluent – Extract		Eluent – Raffinate		Recycle (mL/min)	Switching time (min)
Feed (mL/min)	Extract (mL/min)	Feed (mL/min)	Raffinate (mL/min)	Eluent (mL/min)	Extract (mL/min)	Eluent (mL/min)	Raffinate (mL/min)		
2.500	3.240	2.500	7.275	5.628	4.888	5.628	2.870	1.264	26.283
3.000	3.740	3.000	7.775	6.605	5.865	6.605	3.444	1.517	31.540
3.500	4.240	3.500	8.275	7.583	6.843	7.583	4.018	1.770	36.796
4.000	4.740	4.000	8.775	8.560	7.820	8.560	4.592	2.023	42.053
4.500	5.240	4.500	9.275	9.538	8.798	9.538	5.166	2.276	47.309
5.000 <sup>a</sup>	5.740 <sup>a</sup>	5.000 <sup>a</sup>	9.775 <sup>a</sup>	10.515 <sup>a</sup>	9.775 <sup>a</sup>	10.515 <sup>a</sup>	5.740 <sup>a</sup>	2.529 <sup>a</sup>	52.566 <sup>a</sup>
5.500	6.240	5.500	10.275	11.493	10.753	11.493	6.314	2.781	57.822
6.000	6.740	6.000	10.775	12.470	11.730	12.470	6.888	3.034	63.079
6.500	7.240	6.500	11.275	13.448	12.708	13.448	7.462	3.287	68.336
7.000	7.740	7.000	11.775	14.425	13.685	14.425	8.036	3.540	73.592
7.500	8.240	7.500	12.275	15.403	14.663	15.403	8.610	3.793	78.849

Langmuir isotherm of phenylalanine		Langmuir isotherm of tryptophan	
a	b	a	b
0.998	0.00101	7.130	0.00198
1.197	0.00228	8.556	0.00446
1.397	0.00514	9.982	0.0100
1.597	0.0116	11.408	0.0226
1.796	0.0260	12.834	0.0508
1.995 <sup>a</sup>	0.0585 <sup>a</sup>	14.260 <sup>a</sup>	0.114 <sup>a</sup>
2.195	0.132	15.686	0.257
2.394	0.296	17.112	0.579
2.594	0.666	18.538	1.30
2.793	1.50	19.964	2.93
2.993	3.37	21.390	6.59

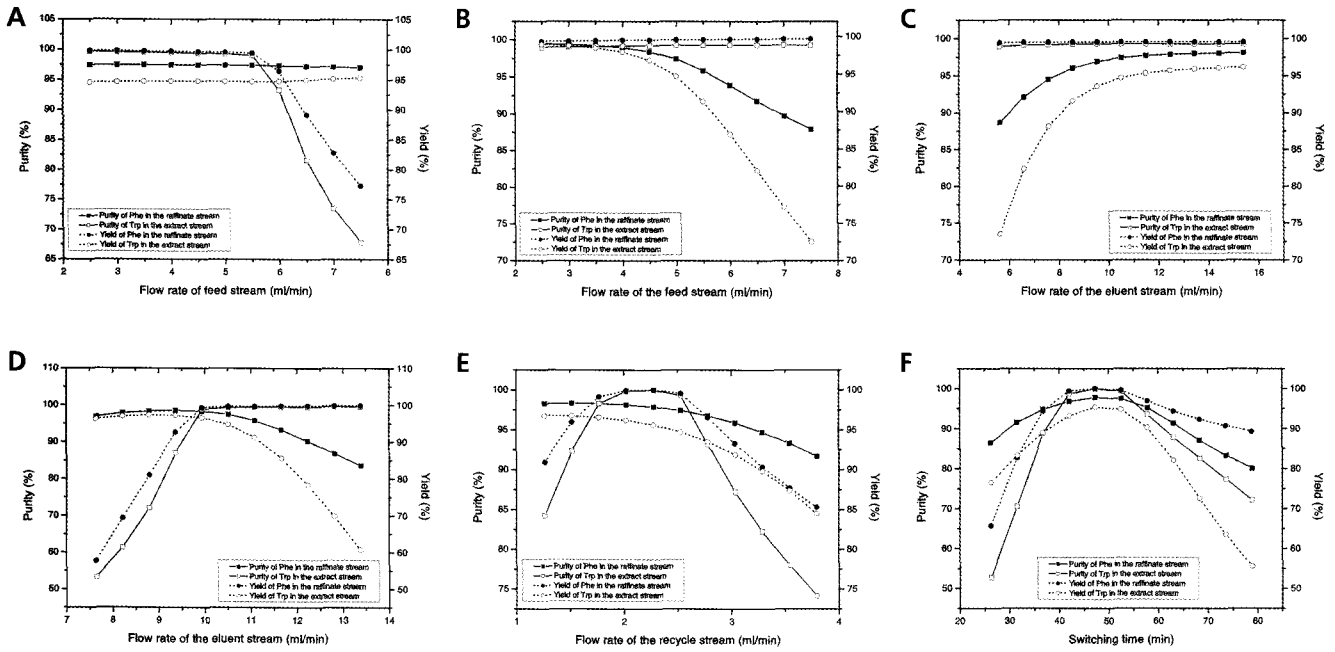
<sup>a</sup> Standard operating condition.



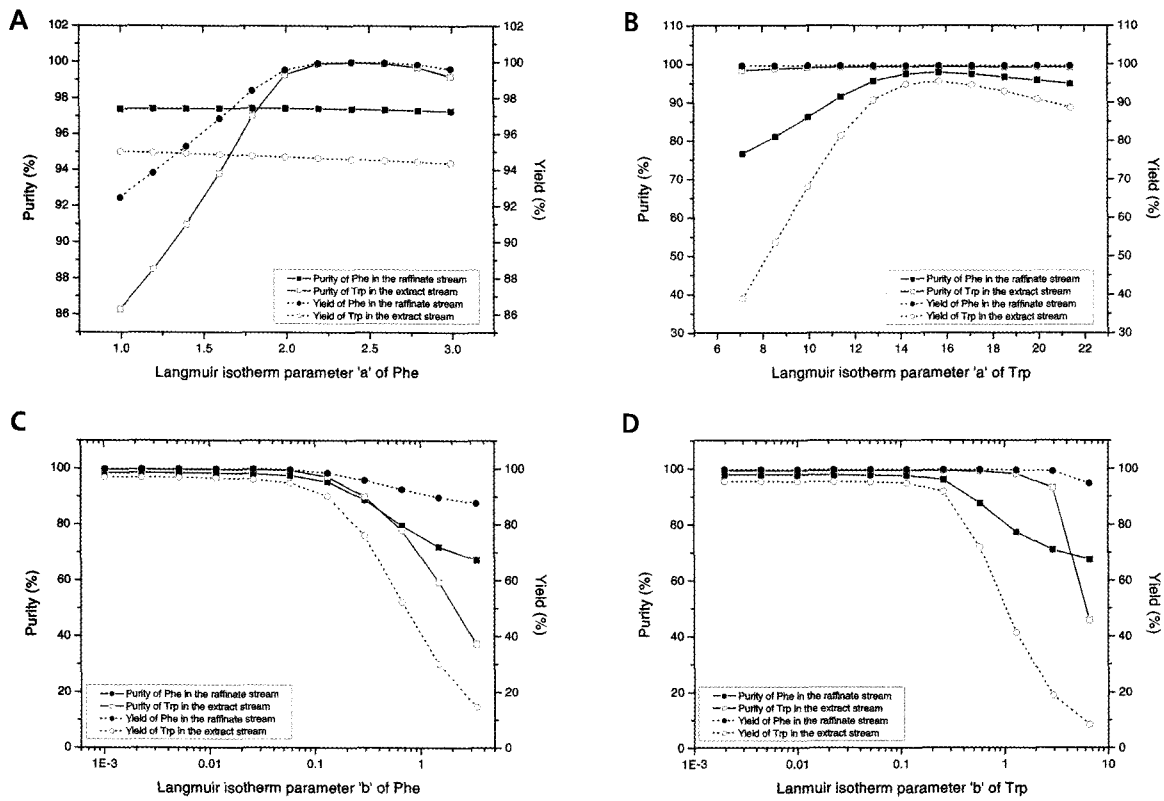
**Fig. 1.** The  $m_2$ - $m_3$  plane of the triangle theory. The open circle denotes the standard condition.

four zone flow rates were changed simultaneously. In the eluent-raffinate scenario, the flow rates of zone I, zone II, and zone III are decreased with eluent stream flow rate. In the recycle and the switching time scenarios, all four zone flow rates dropped as the recycle flow rate was lowered and the switching time was shortened. Fig. 2D sums up the effect of the feed-extract, the feed-raffinate, and the eluent-extract scenarios. Fig. 2E and F demonstrate that the purities and yields of Phe and Trp diminished as the flow rate of recycle stream or the switching time departed from standard conditions. The purity of Phe and the yield of Trp, however, were improved for slow flow rate of recycle. Under standard operating conditions, the flow rate of eluent stream (10.515 mL/min) was faster than the flow rate of recycle stream (2.529 mL/min). This means that the zone I flow rate can be kept high despite a very low recycling flow rate preventing Trp to travel into zone IV or zone III.

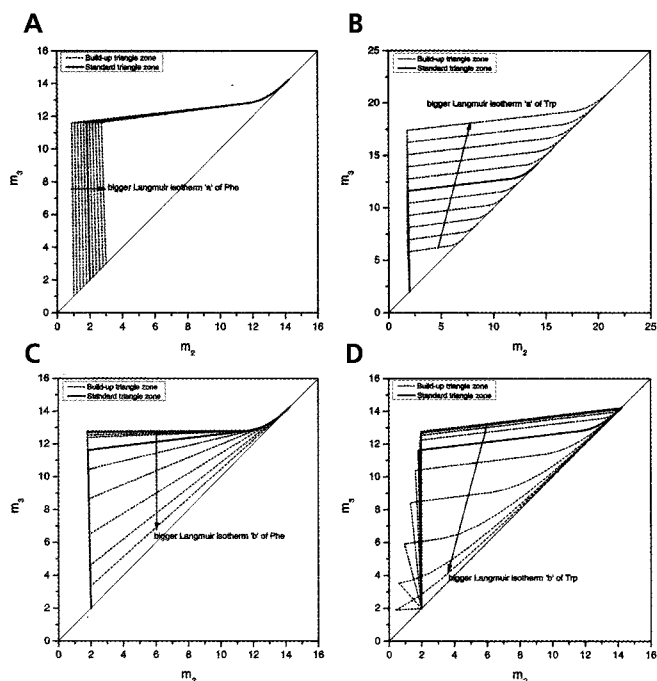
Fig. 3 shows the changes of purity and yield of products with the Langmuir isotherm parameter changes



**Fig. 2.** Changes of the purity and yield of products. Closed symbols are the data of Phe and open symbols are the data of Trp. Solid lines are the purities of the products and dotted lines are the yields of the products. (A) feed-extract, (B) feed- raffinate, (C) eluent-extract, (D) eluent-raffinate, (E) recycle, and (F) switching time.



**Fig. 3.** Changes of the purity and yield of products. Closed symbols are the data of Phe and open symbols are the data of Trp. Solid lines are the purities of the products and dotted lines are the yields of the products. (A) Langmuir isotherm parameter  $a$  for Phe, (B) Langmuir isotherm parameter  $a$  for Trp, (C) Langmuir isotherm parameter  $b$  for Phe, and (D) Langmuir isotherm parameter  $b$  for Trp.



**Fig. 4.** Changes of the triangle zone. Solid lines delineate the triangle zones under standard operating conditions. Dotted lines refer to variable isotherm parameters. (A) Langmuir isotherm parameter  $a$  for Phe, (B) Langmuir isotherm parameter  $a$  for Trp, (C) Langmuir isotherm parameter  $b$  for Phe, and (D) Langmuir isotherm parameter  $b$  for Trp.

(Langmuir isotherm parameter  $a$  and  $b$  for Phe and Trp, respectively, and vice versa). Fig. 4 illustrates the changes of triangle region in  $m_2$ - $m_3$  plane. Fig. 3A shows that the purity of Trp and the yield of Phe worsened when low Langmuir isotherm parameter  $a$  was used for Phe. As shown Fig. 4A, the triangle region fluctuated only very little. The operating condition was therefore maintained within the separation region of  $m_2$ - $m_3$  plane. A lower Langmuir isotherm parameter  $a$  for Phe also caused a faster than standard migration velocity, resulting in Phe remained in the zone IV being moved to zone II via the zone I. Purity of Phe and yield of Trp also worsened as the Langmuir isotherm parameter  $a$  for Trp diverged from the standard value (Fig. 3B). The diminutions in the region of small  $a$  for Trp are more larger than those in the region of big  $a$  for Trp. As shown Fig. 4B, The triangle region was highly variable, which prevented operation within the separation region of the  $m_2$ - $m_3$  plane. Bigger value of the Langmuir isotherm parameter  $a$  for Trp slowed the migration velocity to substandard value resulting in Trp remained in the zone I being moved to zone III via zone IV. Purity and yield of products dropped for bigger Langmuir isotherm parameters  $b$  for both, Phe and Trp (Figs. 3C and D, respectively). The triangle region was more confined for larger Langmuir isotherm parameters  $b$  for both, Phe and Trp (Figs. 4C and D, respectively). Thus, standard operating conditions could not be kept in the triangle zone.

## CONCLUSION

In this work, we considered the sensitivity analysis of conventional SMB chromatography with the operating condition and the Langmuir isotherm parameters. The flow rate ratios of zones were changed by the fluctuations of operating conditions. And changed flow rate ratios influenced the purities and yields of products in the extract and raffinate stream. All flow rate ratios must be maintained within the criteria which are settled by Eqs. (5)~(7). In the sensitivities of operating conditions, the feed- raffinate, the feed-extract, and the eluent-extract cases were less sensitive than the others (the eluent- raffinate, the recycle, and the switching time cases). These less sensitive cases affected only one zone flow rate ratio, but more sensitive cases affected three or all zone flow rate ratios. Therefore, in less sensitive cases, the purities and yields of products became deteriorated as zone flow rate is decreased or increased, but in more sensitive cases, the purities and yields of products also became deteriorated except standard condition. The operating condition criteria (Eqs. (5)~(7)) were determined by the adsorption isotherm parameters [6]. In Langmuir adsorption isotherm model, the fluctuation of isotherm parameter  $b$  had more effect on the purities and yields of products than the isotherm parameter  $a$ .

SMB chromatograph was very difficult to operate and requires preliminary experiments to design the operating conditions. It had many weak points to hold errors or mistakes. We hope that the weak points of SMB chromatography are diminished or vanished by the sensitivity analysis of SMB.

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## NOMENCLATURE

$c$	Concentration of the solute in the mobile phase [mg/mL]
$q$	Concentration of the solute in the stationary phase [mg/mL]
$D_i$	Axial dispersion coefficient [cm <sup>2</sup> /min]
$a$	Langmuir isotherm parameter [-]
$b$	Langmuir isotherm parameter [mL/mg]
$S$	Cross-sectional area of the column [cm <sup>2</sup> ]
$Q$	Volumetric flow rate of the mobile phase [mL/min]

## Greek

$\varepsilon_T$	Total void fraction of the column [-]
$\varepsilon_i$	Interparticle void fraction of the column [-]
$\varepsilon_p$	Intraparticle void fraction of the column [-]

## Subscript

$i, j$	Component index [-]
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*t* Time domain [min]  
*z* Axial domain [cm]

### Superscript

*t* Time domain node index in FDM method  
*z* Axial domain node index in FDM method

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