Continuous Separation of Enantiomers by Simulated Moving Bed Chromatography: Effect of Operating Parameters on the System Performance

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Abstract—The separation of 1,1'-bi-2-naphthol racemic mixtures by the simulated moving bed (SMB) method with chiral columns of Pirkle D-Phenylglycine was investigated in this study. First, a steady-state true moving bed (TMB) model, considering non-linear equilibrium, lumped kinetic and axial dispersion effects, was developed for predicting the cyclic steady-state behavior of the SMB system. The "triangle theory" was used to provide guide-lines for the selection of feasible operating parameters of the SMB system, including liquid flow rates, switch time, feed concentration and zone length. Then, the effect of various operating parameters on the SMB performance, characterized by product purity, recovery, solvent consumption, and productivity, and the exact good separation region were studied through simulation of the TMB model. The package is an important tool to select the optimal operating conditions for the SMB operation.

Key Words : Enantiomers, Chiral columns, Simulated moving bed, System performance, Optimal operation

INTRODUCTION

The simulated moving-bed (SMB) technology developed by UOP (Broughton and Gerhold, 1961) has been used in chemical industry for several bulk large-scale separations known as SORBEX processes (Johnson and Kabza, 1993). They include the separation of *p*-xylene from C8 aromatics (Parex process), the extraction of *n*-paraffins from branched and cyclic hydrocarbons (Molex process), and the recovery of fructose from fructose-glucose mixtures in the production of high fructose corn syrup HFCS (Sarex process). This technology has been recently applied in new areas such as biotechnology, pharmaceuticals, and fine chemistry (Nicoud, 1992).

The separation of enentiomers is an important issue in various areas and particularly in the healthrelated field. The FDA has decided to consider the two enantiomers as two different chemicals for the purpose of their approval as drugs (Anon, 1992). Frequently, the two enantiomers have widely different levels of efficiency and safety. As a consequence, their separation and/or purification is often necessary. SMB is now considered to be the most promising technique for the preparative production of single enantiomeric drugs able to compete to up to now dominating techniques such as elution batch chromatography, diastereoisomeric crystallization, or asymmetric synthesis (Stinson, 1995).

The concept of the SMB is based in the true moving bed (TMB) process, where the liquid goes up and solid goes down in each zone, and then countercurrent contact between solid and liquid occurs, leading to a high mass transfer driving force. Unfortunately, the concept cannot really be implemented because of operating problems associated with the solid circulation in a TMB unit. In the SMB technology, the countercurrent movement is simulated by an appropriate flow switching sequence: the adsorbent bed is divided into a number of fixed-bed columns, while the inlet (eluent and feed) and outlet (extract and raffinate) lines move simultaneously one column at fixed switch time intervals in the direction of the fluid phase flow. Hence, it has the main advantage of being a continuous process able to perform high purity and recovery for low selectivity separations with reductions in eluent consumption and adsorbent requirements when compared with batch chromatography (Balannec and Hotier, 1993).

Successful operation of a SMB process depends on the appropriate choice of the operating conditions, particularly on the internal and external flow rates, switch time, feed concentration and bed geometry. Modeling and simulation of the SMB separation processes have gained increasing attention because they could lead to significant saving in material and time as the operating parameters could be determined during the technology development stage itself.

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Models available in the literature for SMB separation processes have been summarized by Ruthven and Ching (1989). There are two main strategies of modeling SMB processes: one is the real SMB model and the other is the equivalent TMB model. Although small differences appear between these two strategies, the prediction of the performance of a SMB operation can be done using the TMB approach (Pais *et al.*, 1997, 1998). The so-called "triangle theory", based on the TMB approach, provides explicit criteria for the choice of the proper operating conditions for both linear and non-linear systems (Mazzotti et al., 1997; Gentilini et al., 1998; Migliorini et al., 1998). However, it has been developed under ideal conditions (axial dispersion and mass transfer resistance neglected). When mass-transfer effects are present, the complete separation region is considerably reduced and it is only possible to define the region in terms of flow-rate ratio constraints through simulation (Azevedo and Rodrigues, 1999).

The continuous separation of enantiomers of 1-1'-bi-2-naphthol in the chiral columns of Pirkle D-Phenylglycine using hexane-IPA (90:10) as eluent by using the four-column SMB method was considered as a model system in this study. The objective is to describe the operating conditions that lead to an optimal performance of the process. First, a TMB model, considering non-linear equilibrium, lumped kinetic and axial dispersion effects, was developed. Then, the "triangle theory" was used to provide guidelines for the selection of the feasible operating conditions and the effect of the various operating parameters was studied through TMB model simulation. Finally, optimal operation strategies of this system were proposed.

THEORY

True moving-bed strategy of modeling

The model used in this study for the prediction of the cyclic steady-state performance of the SMB was developed based on the equivalent TMB model. The following assumptions are made: the adsorbent is homogeneous, the flow pattern for the fluid and solid phases can be described by plug flow, the dead volumes at both ends of the packed column are negligible, and the mass transfer between fluid and particle can be described by the linear driving force (LDF) model (Glueckauf, 1955).

Model equations for the steady-state TMB unit are summarized in Table 1, where i (i = A, B) refers to the species in the mixture and j (j = I, II, III, IV) refers to the zone number, C_{ij} and q_{ij} are the fluid-phase and average-solid-phase concentrations of species *i* in zone *j*, respectively, q_{ij}^{\dagger} is the corresponding solid-phase concentration in equilibrium with C_{ij} , v_j is the interstitial fluid velocity in zone j, k_i is the lumped mass transfer coefficient of species i between the fluid and the adsorbent, D_{Li} is the axial dispersion coefficient in zone j, ε is the column porosity, u_s is the equivalent interstitial solid velocity in the TMB process, z is the direction of the fluid phase flow, L_i is the length of zone j, and $x = z/L_i$. The dimensionless model parameters are defined as: F = $(1 - \varepsilon)/\varepsilon$ (phase ratio), $\alpha_{ij} = k_i L_j / v_j$ (number of overall mass transfer units of species *i* in zone *j*), $Pe_j =$ $v_i L_i / D_{Li}$ (Peclet number of zone *j*) and $\gamma_i = v_i / u_s$ (ratio between fluid and solid velocities of zone *j*).

The steady-state TMB model equations, Eqs. (T-1) and (T-2), supplemented with boundary conditions, were solved numerically using the finite difference method. The resulting coupled nonlinear algebraic equations were solved using subroutine

Table 1. Model equations for the steady-state TMB.

- Mass balance in the fluid phase: $0 = \frac{1}{Pe_{i}} \frac{d^{2} C_{ij}}{dx^{2}} - \frac{d C_{ij}}{dx} - F\alpha_{ij}(q_{ij}^{*} - q_{ij})$
- Mass balance in the solid phase:

$$0 = \frac{\mathrm{d} q_{ij}}{\mathrm{d} x} + \alpha_{ij} \gamma_j (q_{ij}^* - q_{ij}) \tag{T-2}$$

(T-1)

• Boundary conditions for zone *j*:

$$x = 0: C_{ij} - \frac{1}{Pe_j} \frac{dC_{ij}}{dx} = C_{ij,0}$$
(T-3)

• Nonlinear equilibrium isotherms: $q_{ij}^* = f_i(C_{Aj}, C_{Bj})$ (T-4)

• Species mass balances at the nodes of the four zones: (x = 1)

$$C_{i \text{ IV}}\Big|_{z=L_{\text{IV}}} = \frac{v_{\text{I}}}{v_{\text{IV}}} C_{i \text{ I}}\Big|_{z=0} \quad \text{(eluent node)} \qquad (\text{T-5a})$$

$$C_{i II}|_{z=0} = C_{i I}|_{z=L_{I}}$$
(extract node) (T-5b)
$$C_{i II}|_{z=L_{II}}$$

$$= \frac{v_{\text{III}}}{v_{\text{II}}} C_{i \text{ III}} \Big|_{z=0} - \frac{v_F}{v_{\text{II}}} C_i^F \quad \text{(feed node)} \qquad \text{(T-5c)}$$
$$C_{i \text{ IV}} \Big|_{z=0} = C_{i \text{ III}} \Big|_{z=L_{\text{III}}} \qquad \text{(raffinate node)} \qquad \text{(T-5d)}$$

(raffinate node)

(T-5d)

and

$$q_{ij}|_{z=L_j} = q_{ij+1}|_{z=0}$$
 (each node) (T-5e)

• Overall mass balances at the nodes of the four zones:

$v_{\rm I} = v_{\rm IV} + v_D$	(eluent node)	(T-6a)
$v_{\rm II} = v_{\rm I} - v_E$	(extract node)	(T-6b)
$v_{\rm III} = v_{\rm II} + v_F$	(feed node)	(T-6c)
$v_{\rm IV} = v_{\rm III} - v_R$	(raffinate node)	(T-6d)

Note: i = A, B (species in the mixture),

j = I, II, III, IV (zone no.),

- A: more-retained species; B: less-retained species;
- *E*: extract; *R*: raffinate; *F*: feed; *D*: eluent;

 $C_{ii,o}$: inlet concentration of species *i* in zone *j*.

C05NBF implemented in the NAG foundation of Matlab toolbox. It is based upon the MINPACK routine HYBRD1, a modification of the Powell hybrid method (Powell, 1970).

Design of a simulated moving-bed

Successful operation of SMB depends on the correct choice of the operating conditions, particularly on the internal flow rates and the switch time. As the degree of subdivision of a SMB unit increases, the system performance of a SMB model approaches to that of a TMB model (Pais *et al.*, 1998). Therefore, the operating conditions of a SMB separator can be optimized using the TMB approach.

The design problem of a TMB consists on setting the proper operating conditions (liquid and solid flow-rates) to obtain the desired separation. In order that the less retained species moves in the direction of the liquid phase and the more retained one in the direction of the solid phase, some constraints have to be satisfied in each column. The constraints, defining a complete separation in a TMB unit for a linear equilibrium binary system in the absence of dispersion and mass-transfer effects, can be expressed as (Ruthven and Ching, 1989; Zhong and Guiochon, 1996):

$$\frac{Q_{I}C_{AI}}{Q_{s}q_{AI}} > 1;$$

$$\frac{Q_{II}C_{BII}}{Q_{s}q_{BII}} > 1 \quad \text{and} \quad \frac{Q_{II}C_{AII}}{Q_{s}q_{AII}} < 1;$$

$$\frac{Q_{III}C_{BIII}}{Q_{s}q_{BIII}} > 1 \quad \text{and} \quad \frac{Q_{III}C_{AIII}}{Q_{s}q_{AIII}} < 1;$$

$$\frac{Q_{IV}C_{BIV}}{Q_{s}q_{BIV}} < 1,$$
(1)

where Q_j is the internal liquid flow rate in zone j, $Q_j = v_j A_c \varepsilon$, Q_s is the equivalent interstitial solid flow rate in the TMB process, $Q_s = u_s A_c (1 - \varepsilon)$, and A_c is the column area. The same constraints can be expressed alternatively in terms of fluid and solid velocities. Defining the parameter γ_j as the ratio between fluid and solid velocities of zone j, *i.e.*, $\gamma_j = v_j/u_s$, the constraints defined by Eq. (1) becomes:

$$\begin{aligned} \gamma_1 > FK_A; \quad FK_B < \gamma_{II} < FK_A; \\ FK_B < \gamma_{III} < FK_A; \quad \gamma_{IV} < FK_B, \end{aligned}$$
(2)

where $K_i = q_{ij}/C_{ij}$ is the Henry's constant of species *i* which is the same for each zone.

These constraints are in accordance with the equilibrium model results first proposed by Storti *et al.* (1993). In a $\gamma_{II} \times \gamma_{III}$ plane, this region corresponds to the square triangle shown in Fig. 1. Inside this

square triangle, any $(\gamma_{II}, \gamma_{III})$ pair yields complete separation provided the constraints on γ_1 and γ_{V} are not violated. The above region of complete separation has been developed under linear and ideal (axial dispersion and mass transfer resistance neglected) conditions. When non-linearity and mass-transfer effects are present, it is only possible to define these limits through simulation. Figure 1 also shows the true region of complete separation, which might be twisted leftward and downward and significantly reduced. The deformation is due to the non-linear equilibrium, as shown by the simulations of Mazzotti et al. (1997), Gentilini et al. (1998), and Migliorini et al. (1998), while the reduction is due to the non-ideal conditions, as shown by the simulation of Azevedo and Rodrigues (1999). Nevertheless, the ideal region of complete separation, which is easily formed by using the equilibrium Henry's constant of each isomer, can be referred to find the good operating conditions.

The liquid flow rates in a TMB process include the four internal liquid flow rates: $Q_{\rm I}, Q_{\rm II}, Q_{\rm III}, Q_{\rm IV}$ (or $Q_{recycle}$) and the four external flow rates: Q_F , Q_D , Q_E , Q_R , which are related by the overall mass balances at the nodes of the four zones. Therefore, there are only four independent variables among them and Q_F , Q_D , Q_E (or Q_R) and $Q_{recycle}$ are usually selected as the adjustable parameters of the process (Jura, 1999). The four liquid flow rates together with the solid flow rate (Q_s) have to be properly chosen around the ideal region of complete separation. Finally, since both SMB and TMB systems have similar cyclic steady- state performances, the estimation of TMB operating conditions can be applied for the SMB. The rotation period (or switch time) t_s in SMB operation can be calculated from the solid velocity of TMB by: $u_s = L_c / t_s$, where L_c is the column length. The liquid velocities or flow rates v_j^* or Q_j^* of SMB in four zones are evaluated by: $v_i^* = v_i + u_s$ or $Q_i^* = Q_i + u_s$ Q_s/F .



Fig. 1. The ideal and true regions of complete separation in a $\gamma_{II} \times \gamma_{III}$ plane.

Process performance parameters

The SMB performance is characterized by four process parameters: purity, recovery, solvent consumption, and adsorbent productivity. Table 2 defines the process performance parameters for the case of a binary separation, in which the less retained species B (S-isomer of 1,1'-bi-2-naphthol) is recovered in the raffinate, and the more retained species A (R-isomer of 1,1'-bi-2-naphthol) is recovered in the extract.

Performance Parameters	Extract	Raffinate
Purity (%)	$\frac{\overline{C_{AE}}}{(\overline{C_{AE}}+\overline{C_{BE}})}$	$\frac{\overline{C_{BR}}}{(\overline{C_{BR}}+\overline{C_{AR}})}$
Recovery (%)	$rac{Q_E \overline{C_{AE}}}{Q_F C_{AF}}$	$\frac{Q_R \overline{C_{BR}}}{Q_F C_{BF}}$
Solvent consumption (mL/mg)	$\frac{(Q_F + Q_D)}{Q_E \overline{C_{AE}}}$	$\frac{(Q_F + Q_D)}{Q_R \overline{C_{BR}}}$
Productivity (mg/min)	$Q_E \overline{C_{AE}}$	$Q_R \overline{C_{BR}}$

Table 2. SMB process performance parameters.

Note: A: more-retained species; B: less-retained species; E: extract; R: raffinate; F: feed; D: eluent;

 \overline{C} : time averaged concentration $(0 \sim t_s)$.

SIMULATION RESULTS AND DISCUSSION

The separation system studied in this work is the separation of 1-1'-bi-2-naphthol enantiomers using Pirkle covalent D-phenylglycine (3,5-dinitrobenzoyl

Table 3. Process parameters used in the TMB simulations.

derivative of phenylglycine covalently bonded to aminopropyl silica gel) as chiral stationary phase and mobile phase composition of 90/10 (v/v) hexane/IPA as the eluent.

The process parameters affecting the system performance of a TMB can be grouped into three categories: 1. Design parameters, including column diameter (D_c) , column length (L_c) , particle diameter (d_p) , and bed porosity (ε) ; 2. Operating parameters, including temperature, desorbent composition (hexane/IPA), liquid flow rates $(Q_F, Q_D, Q_E, Q_R, \text{ and}$ $Q_{recycle}^*$), equivalent switch time of the SMB model (t_s) , feed concentration (C_F) , and zone length $(L_j \text{ or } N_j L_c)$; 3. Physicochemical parameters, including dispersion coefficient (D_{Lj}) , overall mass transfer coefficients (k_i) , and adsorption isotherm parameters $(K_i$ *etc.*).

All the above parameters used in our simulations are listed in Table 3. The geometry of the SMB unit set up in our laboratory, four zones with 1 column in each zone and column length of 10 cm, was considered as a reference case in our simulation. The physicochemical parameters were also selected from our previous study (Lai *et al.*, 2000) and fixed for the following simulations. The adsorption equilibrium isotherm of bi-Langmuir type was used:

$$q_R^* = \frac{3.09C_R}{1 + 0.011C_R + 0.00913C_S} + \frac{0.31C_R}{1 + 0.369C_R + 0.345C_S},$$
(3a)

$$q_{S}^{*} = \frac{2.51C_{S}}{1+0.011C_{R}+0.00913C_{S}} + \frac{0.29C_{S}}{1+0.369C_{R}+0.345C_{S}}.$$
(3b)

Physicochemical	Operating	Design
Parameters	Parameters	Parameters
Axial dispersion	<i>Temperature</i> : $T = 30^{\circ}$ C	$D_c = 1.0 \text{ cm}$
coefficient:		
$D_{Lj} = 0.024 \text{ cm}^2/\text{min}$	Desorbent composition (hexane/IPA): 90/10	
Overall mass transfer	Liquid flow rates and	$L_c = 10 \text{ cm}$
coefficient:	Equivalent SMB switch time:	
$k_R = k_S = 6 \text{ min}^{-1}$	$Q_F + Q_D = \text{varied } (2.5 \text{ mL/min}^a)$	$d_p = 10 \ \mu m$
	$Q_F = \text{varied } (0.3 \text{ mL/min}^{\text{a}})$	
	$Q_E = \text{varied} (1.1 \text{ mL/min}^{\text{a}})$	
Linear isotherm:	$Q_{R} = \text{varied} (1.4 \text{ mL/min}^{a})$	$\varepsilon = 0.53$
$K_R = 3.4$	$Q_{recycle}^* = \text{varied} (1.6 \text{ mL/min}^*)$	(F = 0.89)
$K_{S} = 2.8$	$t_s = \text{varied} (5.5 \text{ min}^a)$	
$(\alpha = 1.21)$		
	Feed concentration:	
	$C_F = \text{varied} (0.57 \text{ mg/mL}^{a})$	
Nonlinear isotherm:		
Bi-Langmuir type,	Zone length:	
Eq. (3)	L_j or $N_j L_c$ = varied (10 cm ^a)	

^a Values of the reference case

In the above equations, q_R^* and q_S^* are expressed in mg/mL of adsorbent and C_R and C_S are expressed in mg/mL of solution. The low value of the separation factor, $\alpha = 1.21$, calculated by the retention factors (or Henry's constants) of $K_R = 3.4$ and $K_S = 2.8$ mL of solution/mL of adsorbent, suggests that the separation of the two components is a difficult one to perform. Four liquid flow rates, including total solvent flow rate ($Q_F + Q_D$), feed flow rate (Q_F), extract or raffinate flow rate (Q_E or Q_R), and recycle flow rate of SMB ($Q_{recycle}^*$), together with switch time (t_s), feed concentration (C_F) and zone length (L_j) were selected as the adjustable parameters of the process. Their effects on the system performance were studied by simulation.

Effect on the location in the $\gamma_{II} \times \gamma_{III}$ plane

Using the bed porosity and retention factors of Table 3, the square triangle region of complete separation in the $\gamma_{II} \times \gamma_{III}$ plane, formed by the flow constraints (Eq. (2)) proposed by the linear and ideal model, is plotted and shown in Fig. 2. Due to the equivalence between SMB and TMB approaches, the complete separation region was referred to select the proper operating conditions of the SMB unit.

When the operating conditions, including liquid flow rates and switch time, of a SMB unit are selected, its location in the $\gamma_{II} \times \gamma_{III}$ plane is determined. The set of operating conditions located inside or close to the complete separation region of a TMB unit is supposed to be a good choice, but the exact system performance has to be determined by simulation. It is noted that feed concentration and zone length have no influence on the location of the $\gamma_{II} \times \gamma_{III}$ plane, but they do have a significant effect on the system performance, which will be discussed in the following section.



Fig. 2. Location of the $\gamma_{II} \times \gamma_{III}$ plane from the adjustment of operating conditions close to the complete separation region. Operating conditions for the four lines and the reference case (point A) are referred to Table 4.

Adjustment of operating conditions

Based on the complete separation region in the $\gamma_{\text{II}} \times \gamma_{\text{III}}$ plane, the operating conditions can be adjusted by the following ways. The total solvent flow rate $(Q_F + Q_D)$ was fixed first. A reference case, located inside the complete separation region, was selected and only one of the other operating conditions, including Q_F (or Q_D), Q_E (or Q_R), $Q^*_{recycle}$, and t_s , was varied at each calculation. Table 4 shows the four sets of operating conditions in terms of liquid flow rates and switch time. Their locations in the $\gamma_{\text{II}} \times \gamma_{\text{III}}$ plane are shown in Fig. 2, which were compared to that of the complete separation region. It is worth noting that all the constraints on γ_1 and γ_{IV} of each run were not violated.

Table 4. Adjustment of operating conditions close to the complete separation region. (Reference case (point A): $Q_F+Q_D = 2.5 \text{ mL/min}, Q_F = 0.3 \text{ mL/min}, Q_D = 2.2 \text{ mL/min}, Q_E = 1.1 \text{ mL/min}, Q_R = 1.4 \text{ mL/min}, Q_{recycle} = 1.6 \text{ mL/min}, \text{ and } t_s = 5.5 \text{ min}$).

Line No.	Q_F (mL/min)	Q _D (mL/min)	Q_E (mL/min)	<i>Q</i> _{<i>R</i>} (mL/min)	$Q^*_{recycle}$ (mL/min)	t_s (min)	Location in the $\gamma_{II} - \gamma_{III}$ Plane
1	0.3	2.2	1.1	1.4	1.6	variation: $4.25 \rightarrow 8.0$	_
2	0.3	2.2	1.1	1.4	variation: $0.8 \rightarrow 3.2$	5.5	
3	0.3	2.2	variation: $0.7 \rightarrow 1.5$	variation: $1.8 \rightarrow 1.0$	1.6	5.5	
4	variation: $0.1 \rightarrow 0.5$	variation: $2.4 \rightarrow 2.0$	1.1	1.4	1.6	5.5	←

It is found from Fig. 2 that a straight line was created in the $\gamma_{II} \times \gamma_{III}$ plane for each set crossing the complete separation region and nearly parallel to the diagonal of the $\gamma_{II} \times \gamma_{III}$ plane, except for the set of Q_F variation (Line 4) from which a horizontal line was created. The locations for Line 2 (adjustment of $Q_{recycle}^{*}$) and Line 3 (adjustment of Q_E) were just the same and not too much different from Line 1 (adjustment of t_s). For the sake of easy operation and high reliability, switch time (t_s) of SMB model was selected as the adjustable operating condition for crossing the complete separation region in the following simulations.

Effect of feed flow rate and total solvent flow rate

The effect of total solvent flow rate $(Q_F + Q_D)$ and feed flow rate (Q_F) was then examined. Figure 3



Fig. 3. Effect of feed flow rate and total solvent flow rate on the location of the $\gamma_{II} \times \gamma_{III}$ plane.

- (a) $Q_F + Q_D = 1.0 \text{ mL/min} (Q_E = 0.44 \text{ mL/min}, Q_R = 0.56 \text{ mL/min}, Q_{recycle}^* = 0.64 \text{ mL/min});$ (b) $Q_F + Q_D = 2.5 \text{ mL/min} (Q_E = 1.10 \text{ mL/min}, Q_R = 1.40 \text{ mL/min}, Q_{recycle}^* = 1.60 \text{ mL/min});$
- (c) $Q_F + Q_D = 4.0 \text{ mL/min}$ ($Q_E = 1.76 \text{ mL/min}$, $Q_R = 2.24 \text{ mL/min}$, $Q_{recycle}^* = 2.56 \text{ mL/min}$).

shows the locations in the $\gamma_{II} \times \gamma_{III}$ plane for three cases of total solvent flow rate ($Q_F + Q_D = 1.0, 2.5$, and 4.0 mL/min). For each case, Q_E , Q_R , and $Q^*_{recycle}$ values were fixed (selected proportionally according to their $Q_F + Q_D$ values) and the switch time was changed creating the lines nearly parallel to the diagonal in this figure, as explained above, whereas Q_F value was varied from line to line. It is again noted that all the constraints on γ_I and γ_{V} of each run were not violated.

It is found that, when $Q_F + Q_D$ value is fixed, increasing the feed flow rate, leading to a parallel line more far away from the diagonal line and the complete separation region, could deteriorate the system performance significantly. As $Q_F + Q_D$ value is increased, the location of a higher feed flow rate operation becomes closer to the triangle region, but whether its system performance could be enhanced has to be checked later by simulation.

Effect on the system performance

The complete separation region of the $\gamma_{II} \times \gamma_{III}$ plane, developed under linear and ideal (axial dispersion and mass transfer resistance neglected) conditions, is only a reference for selecting the proper operating conditions. The exact good separation region, when non-linearity and mass-transfer effects are present, has to be found through simulation.

Effect of feed flow rate and switch time

It would be of great interest to see if a proper selection of operating conditions for locating γ_{II} and γ_{III} values inside or close to the triangle region of $\gamma_{\rm II} \times \gamma_{\rm III}$ plane guarantees a better separation. Three sets of simulations were performed with operating conditions in terms of liquid flow rates, Q_F , Q_D , Q_E , Q_R , and $Q^*_{recycle}$, and switch time, t_s . The total solvent flow rate, *i.e.*, $Q_F + Q_D$ value, was fixed (= 2.5 mL/min) for all runs in the three sets, whereas Q_F value was varied from set to set. The operating points of the simulations in the $\gamma_{II} \times \gamma_{III}$ plane are shown in Fig. 4, where their position is compared to that of the square triangle region of complete separation corresponding to the linear and equilibrium model. The liquid flow rates in each of the three sets were kept constant, whereas the switch time was changed. This created a straight line in the $\gamma_{II} \times \gamma_{III}$ plane nearly parallel to the diagonal, as explained above.

The system performance in terms of product purity was then simulated and is shown in Fig. 4. The regions on the $\gamma_{II} \times \gamma_{III}$ plane having different purity requirements were simulated as follows. Starting from the case of low feed flow rate and adjusting the switch time across the square triangle region, the two-point boundary was determined by the desired purity, in which every operating condition inside the





 $Q_F + Q_D = 2.5 \text{ mL/min}, Q_E = 1.10 \text{ mL/min},$ $Q_R = 1.40 \text{ mL/min}, Q_{recycle}^* = 1.60 \text{ mL/min},$ $t_s = 5.0 \sim 6.0 \text{ min}, C_F = 0.57 \text{ mg/mL},$ and $L_j = 10 \text{ cm}.$

boundary possessed product purity higher than the desired purity. The distance between the boundary points reduced and finally disappeared with increasing feed flow rate. Connecting all the boundary points formed the separation region of the desired product purity. The same process was repeated for the different desired product purity. It is found that the exact separation region was significantly reduced due to the mass-transfer effects, which is same as the results simulated by Azevedo and Rodrigues (1999). For the current simulation using zone length of 10 cm, purity higher than 95% could be obtained only at low feed flow rate conditions (< 0.3 mL/min).

The optical purities of the extract and raffinate streams of the three sets predicted by the TMB model were compared and is shown in Fig. 5. The first set had the lowest feed flow rate and its position in the $\gamma_{\rm II} \times \gamma_{\rm III}$ plane corresponded to operating points belonging to the straight line closer to the diagonal line in Fig. 4. By increasing the switch time from 5 minutes to 6 minutes, *i.e.*, across the square triangle region, the purity values shown as a function of the switch time in Fig. 5(a) exhibited the expected pattern of behavior, i.e., the raffinate purity decreased steadily while the extract purity increased. The best overall separation performance achieved was both the extract and raffinate purity of 94.7%. The other two sets had the higher feed flow rates. The system performance as a function of the switch time of the other two sets of experiments, as illustrated in Figs. 5(b) and 5(c), exhibited the same pattern of behavior as the first set in Fig. 5(a). The best overall separa-





tion performance obtained for the extract and raffinate purities were 90% for the second set and 83% for the third set, respectively. Since the feed flow rate in the second and third sets were higher than the first set, they had the higher productivity, *i.e.*, 4.6 mg/h and 7.2 mg/h, respectively, than the productivity of 1.6 mg/h for the first set.

The differences in the system performances among the three sets are as follows. First, the larger the feed flow rate the larger the productivity but the worse the best separation performance achieved, *i.e.*, by reducing the feed flow rate, the product purity can be improved, but the product productivity can be reduced. There must be a compromise between these two performances. Secondly, the range of operating conditions achieving best product purity of each set becomes smaller when increasing the feed flow rate, *i.e.*, the separation conditions become less robust, which means the proper selection of the switch time is very important.

Effect of total solvent flow rate

Figure 6 shows the system performances in terms of product purity for the cases of $Q_F + Q_D$ values of 1.0 and 4.0 mL/min, respectively. Again, the regions on the $\gamma_{II} \times \gamma_{III}$ plane having different purity requirements were simulated. The effect of total solvent flow rate on the system performance can be compared between Figs. 4 and 6. It is found that in-

creasing the total solvent flow rate, with which although the location of a higher feed flow rate operation became closer to the triangle region, caused a significant reduction of the good separation region and a less robust operation.

Table 5 shows the comparison of the best system performance, with respect to product purity, of the three cases of total solvent flow rate. It can be seen that the productivity increased but the best product purity decreased and the solvent consumption increased as the total solvent flow rate ($Q_F + Q_D$) and feed flow rate (Q_F) increased. Figure 7 shows the effect of the total solvent flow rate on the best system performance at a feed flow rate of 0.3 mL/min. It is found that, due to the significant reduction of the



Fig. 6. Regions of separation in terms of product purity. Other operating conditions: $C_F = 0.57 \text{ mg/mL}$, $L_j = 10 \text{ cm}$, and (a) $Q_F + Q_D = 1.0 \text{ mL/min}$, $(Q_E = 0.44 \text{ mL/min}$, $Q_R = 0.56 \text{ mL/min}$, $Q_{recycle}^* = 0.64 \text{ mL/min}$, $t_s = 12.0 \sim 17.0 \text{ min}$); (b) $Q_F + Q_D = 4.0 \text{ mL/min}$, $(Q_E = 1.76 \text{ mL/min}$, $Q_R = 2.24 \text{ mL/min}$, $Q_{recycle}^* = 2.56 \text{ mL/min}$, $t_s = 3.0 \sim 4.0 \text{ min}$).

Table 5. Comparison of the best system performance, with respect to product purity, of the three cases of total solvent flow rate. Other operating conditions: $C_F = 0.57 \text{ mg/mL}$, and $L_j = 10 \text{ cm}$.

	Total Solvent Flow Rate $Q_F + Q_D$ (mL/min)									
		1.0			2.5			4.	0	
Performance	Q_F (mL/min)		Q_F (mL/min)			Q_F (mL/min)				
Parameters	0.05	0.10	0.30	0.10	0.30	0.50	0.10	0.30	0.50	0.80
		t_s (min)			t_s (min)			t_s (n	nin)	
	13.25	13.50	14.86	5.27	5.45	5.66	3.26	3.33	3.4	3.52
Purity R (%)	99.78	98.62	74.81	94.68	90.21	83.62	87.29	85.52	82.97	78.76
Purity S (%)	99.78	99.13	74.86	94.66	90.30	83.22	87.86	85.71	83.44	79.01
Recovery R (%)	99.78	99.13	74.89	94.66	90.31	83.12	87.96	85.75	83.56	78.67
Recovery S (%)	99.78	98.62	74.78	94.68	90.20	83.72	87.19	85.48	82.85	78.50
Solvent consumption <i>R</i> (mL/mg)	70.00	35.24	15.55	92.24	32.22	21.00	158.82	54.30	33.44	22.40
Solvent consumption <i>S</i> (mL/mg)	70.00	35.42	15.57	92.22	32.26	20.86	160.22	54.46	33.72	22.40
Productivity <i>R</i> (mg/h)	0.86	1.70	3.86	1.63	4.65	7.14	1.51	4.42	7.18	10.87
Productivity S (mg/h)	0.86	1.70	3.85	1.63	4.65	7.19	1.50	4.41	7.12	10.87

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Fig. 7. The best system performance: (a) purity; (b) recovery; (c) solvent consumption; (d) productivity, of the extract and raffinate streams as a function of the total solvent flow rate.
-----: S-isomer (raffinate port); ----: R-isomer (extract port).

Other operating conditions: $C_F = 0.57 \text{ mg/mL}$, $L_j = 10 \text{ cm}$, and $Q_F = 0.3 \text{ mL/min}$.

good separation region with increasing the total solvent flow rate, there was an optimal $Q_F + Q_D$ value at which the product purity and productivity were optimized. Once again, there must be a trade-off among the system performances and a proper selection of $Q_F + Q_D$ and Q_F values becomes imperative. For the current simulation, purity higher than 90% and productivity higher than 4.5 mg/h could be obtained at a feed flow rate of 0.3 mL/min and a total solvent flow rate of 2.5 mL/min.

Effect of feed concentration

The feed concentration, although having no influence on the location of the $\gamma_{II} \times \gamma_{III}$ plane, has a significant effect on the system performance. Figure 8 shows the effect of feed concentration on the system performance in terms of product purity. It is found that the exact separation region was twisted leftward and downward due to the non-linear equilibrium and the operation became less robust, which is same as the results simulated by Mazzotti *et al.* (1997), Gentilini *et al.* (1998) and Migliorini *et al.* (1998). The optimal switch time has to be adjusted according to the twisted separation region.



- Fig. 8. Effect of feed concentration on the system performance in terms of product purity (90%). Other operating conditions: $Q_F + Q_D = 2.5 \text{ mL/min}, Q_E = 1.1 \text{ mL/min},$ $Q_R = 1.4 \text{ mL/min}, Q_{recycle}^* = 1.6 \text{ mL/min},$
 - Q_F , t_s = varied values, and L_i = 10 cm.

For the current simulation, the effect of nonlinear equilibrium was not too significant due to the small variation in feed concentration. The feed concentration was restricted by the limit of solubility, which is 3.72 mg/mL in the mobile phase composition of 90/10 (v/v) hexane/IPA from our previous study (Lai *et al.*, 2000). Keeping the same $Q_F + Q_D$ and Q_F values and setting the optimal switch time, the productivity increased almost proportionally with increasing the feed concentration at the expense of product purity (slight reduced) and ease of operation (less robust).

Effect of zone length

For the current simulation, a further improvement in the product purity was limited due to the operation using zone length of 10 cm. The zone length (L_j) was then adjusted and its effect on the system performance is shown in Fig. 9 for 90% purity requirement. It is found that increasing the zone length enlarged the region of good separation, subsequently increased the productivity at the desired product purity and leaded to a more robust separation. However, the improvement in the system performance became less significant as the zone length was further increased. Therefore, the zone length must be selected based on the compromise between the improved system performance and the column cost.



Fig. 9. Effect of zone length on the system performance in terms of product purity (90 %). Other operating conditions:

 $Q_F + Q_D = 2.5 \text{ mL/min}, Q_E = 1.1 \text{ mL/min},$ $Q_R = 1.4 \text{ mL/min}, Q_{recycle}^* = 1.6 \text{ mL/min},$ $Q_F, t_s = \text{varied values, and } C_F = 2.28 \text{ mg/mL}.$

CONCLUSION

A model for predicting the cyclic steady-state behavior of the SMB was developed using the corresponding TMB approach, in which non-linear equilibrium, lumped kinetic and axial dispersion effects were considered. The model can be used to study the effect of operating parameters on the system performance and the good operating conditions for the SMB operation can then be selected.

The SMB geometry of four zones with $1 \sim 3$ columns in each zone and column length of 10 cm is usually adopted for continuous separation of enantiomers. The number of columns in each zone, *i.e.*, the zone length in the TMB model, is determined by considering both the improved system performance and the column cost (Fig. 9).

Once the geometry of the SMB unit is set, the system can be optimized by properly adjusting the liquid flow rates, switch time and feed concentration. The complete separation region in the $\gamma_{II} \times \gamma_{III}$ plane, *i.e.*, the so called "triangle theory", can be used to provide guidelines for the selection of the feasible operating conditions. However, the exact good separation region, when non-linearity and mass-transfer effects are present, has to be found through simulation.

The location in the $\gamma_{II} \times \gamma_{III}$ plane (Fig. 3) and the system performance (Figs. 4 and 6) are most sensitive to the total solvent flow rate $(Q_F + Q_D)$ and feed flow rate (Q_F) . When $Q_F + Q_D$ and Q_F values are fixed, the switch time is usually used as the adjustable operating condition for the adjustment of the location in the $\gamma_{II} \times \gamma_{III}$ plane (Fig. 2) and the system performance (Fig. 5). The product purity being the most concern in the system performance must be met above the desired value (e.g., 95%). The productivity is proportional to Q_F value and the solvent consumption is proportional to $Q_F + Q_D$ value. The product purity can be improved at the expense of the other system performances, including productivity and solvent consumption. $Q_F + Q_D$ and Q_F values must be optimally selected based on the compromise among the product purity, productivity and solvent consumption (Table 5 and Fig. 7).

Finally, when the effect of non-linear equilibrium due to the increase in the feed concentration is not too severe, the feed concentration is suggested to go as high as its solubility limit. The productivity can be increased almost proportionally with increasing the feed concentration and the product purity is only slight reduced (Fig. 8). In case that the effect of non-linear equilibrium is severe, the exact separation region might be twisted severely toward the diagonal of the $\gamma_{\rm II} \times \gamma_{\rm HI}$ plane as predicted by Mazzotti *et al.* (1997), Gentilini *et al.* (1998), and Migliorini *et al.* (1998). The increase in the feed concentration has to

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be optimized together with the optimal selection of $Q_F + Q_D$ and Q_F values.

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NOMENCLATURE

C	fluid-phase concentration, mg/mL of
5	solution
D_c	column diameter, cm
D_L	axial dispersion coefficient, cm ² /min
d_p	particle diameter, µm
F	phase ratio, $F = (1 - \varepsilon)/\varepsilon$, mL of
	adsorbent/mL of solution
K_i	Henry's constant of species <i>i</i> , mL of
	solution/mL of adsorbent
k_i	lumped mass transfer coefficient of the
	species <i>i</i> between the fluid and the
	adsorbent, 1/min
L_c	column length, cm
L_i	length of zone <i>j</i> , cm
Ň _i	number of columns in zone <i>j</i>
Pe_i	Peclet number of zone <i>j</i> in the TMB
5	model, $Pe_i = v_i L_i / D_{L_i}$
0	external fluid flow rate and internal
~	fluid flow rate in the TMB model,
	mL/min
O^{*}	internal fluid flow rate in the SMB
2	model, mL/min
$O_{\rm s}$	equivalent solid flow rate in the TMB
23	model. mL/min
a	mean solid-phase concentration. mg/mL
1	of adsorbent
<i>a</i> *	corresponding solid-phase concentration
1	in equilibrium with C, mg/mL of
	adsorbent
t.	switch time in the SMB model, min
U.	equivalent interstitial solid velocity in
S	the TMB model. cm/min
v	interstitial fluid velocity in the TMB
	model, cm/min
<i>v</i> [*]	interstitial fluid velocity in the SMB
	model cm/min
r	dimensionless position coordinate of
	each zone $r = z/L_{c}$
7	nosition coordinate of each zone cm
4	position coordinate of each zone, em
C]

Greek symbols

α	separation factor
$lpha_{ij}$	number of overall mass transfer units of

species <i>i</i> in zone <i>j</i> in the TMB model,
$\alpha_{ij} = k_i L_j / v_j$
ratio between fluid and solid velocities
of zone <i>j</i> in the TMB model, $\gamma_i = v_i/u_s$
column packing porosity

Subscripts

A	more retained species (R isomer)
В	less retained species (S isomer)
D	desorbent stream
Ε	extract stream
F	feed stream
i	species $i, i = R$ isomer (species A) or S
	isomer (species B)
j	zone number, $j = I$, II, III, IV
R	raffinate stream
recycle	recycle stream

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」以模擬移動床層析法連續分離定比性異構物: 操作參數對系統性能的影響

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搖 ヲ

本研究探討以 Pirkle D-Phenylgycine 型的旋光性管柱所組成之模擬移動床 (SMB) 層析系統連續分離 1-1'-bi-2-naphthol 混旋物的分離性能。首先,建立一個考慮具有非線性平衡以及綜合質傳阻力與軸向擴散等效應之穩態真實移動床 (TMB) 模式,此 TMB 模式可以用來預測 SMB 系統的週期性穩態行為。利用「三角理論」來規劃選取 SMB 系統的操作參數,包括:各液相流量、切換時間、進料濃度、以及區長等。然後,透過此 TMB 模式的模擬分析,可以探討這些操作參數對 SMB 系統性能 (包括:純度、回收率、溶劑耗量以及產率等) 的影響,並進一步找出系統的較佳操作區域。這套分析工具可以用來選取 SMB 系統的最佳操作條件。