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Enantioseparation by Simulated Moving Bed Chromatography: Modeling, Simulation and Operation

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Abstract: The paper deals with chiral separation by Simulated Moving Bed chromatography. A model for the prediction of the cyclic steady-state performance of the SMB, based on the analogy with the true moving bed, is developed assuming multicomponent adsorption equilibria, axial dispersion flow and the linear driving force approximation to describe the intraparticle mass transfer rate. The simulation package is used to predict the effect of operating variables on the process performance and to define the regions for enantiomers separation. The influence of mass transfer resistance in the separation region is analyzed. A practical tool for choosing the better SMB operating conditions as a function of the feed flow rate is proposed. The operation of a pilot unit of SMB, *Licosep 12-26 (Novasep, France)*, is carried out for the separation of bi-naphthol enantiomers. Experimental results and model predictions are compared in terms of process performance and internal concentration profiles.

1. Introduction

The simulated moving bed (SMB) technology [1-3] is receiving an increasing interest as an alternative technique for the production of fine chemicals and pharmaceuticals. Recent works proved the efficiency of this technology at lab scale, and first industrial applications have been mentioned. Following the new regulations regarding the approval of new pharmaceutical drugs, SMB chromatographic separation systems have been developed in order to obtain single enantiomer drugs.

The SMB process basic principle is a flow scheme that takes advantages of continuous and countercurrent movement of liquid and solid without actual movement of the adsorbent. This countercurrent movement is simulated by an appropriated flow switching sequence: the adsorbent bed is divided into a number of fixed-bed columns, while the inlet and outlet lines move simultaneously one column at fixed time intervals in the direction of the liquid phase flow. Hence, the SMB process shares the same advantages of the real countercurrent scheme, bypassing the obvious problems concerning the solid movement. SMB chiral chromatography is, in this way, a 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. SMB chromatography is essentially a binary mixture separation technique, hence particularly suitable for racemic resolutions. Among the main advantages of the SMB chromatography are the fact that is a continuous process able to perform high purity and recovery for low selectivity separations with reductions in eluent consumption and adsorbent requirements.

The main problem of the SMB operation consists in choosing the right solid (switch time interval) and liquid flow rates. Designed for high productivity separations, SMB units usually operate at high feed concentrations leading to non-linear competitive adsorption behaviours. Therefore, modeling and simulation tools are of crucial importance before running the system. This requires a knowledge of some basic information on equilibrium and kinetic parameters.

2. SMB Strategies of Modeling

Different models to predict the performance of a SMB separation process have been proposed in the literature [4]. Two main strategies can be carried out to model a SMB system: one, the SMB model, that considers the real shift of the injection and collection points, the other, the TMB (true moving bed) model, that considers liquid and solid flow in opposite directions. The prediction of these two models were compared in terms of steady-state performance and the influence of the degree of subdivision of the bed in the SMB model predictions was also analyzed and compared with the TMB performance. A complete study, with comparison between experimental and model results, can be found elsewhere [5]. The main conclusion of this study is that the deviations between TMB and SMB predictions (averaged over a switch time interval) decrease as the degree of subdivision of the bed increases. For practical purposes, optimization and choice of SMB configuration (length of each section) can be safely carried out on the basis of analogy with TMB modeling.

Although transient evolution of the SMB and TMB approaches are different, they have similar steady-state performances. Since the primary objective is to characterize steady-state performance, one can simulate and obtain the optimum operating conditions for the SMB using the steady-state TMB model. Thereby, the problem consisting in a PDEs system can be reduced to an ODEs system, which requires lower computing times.

The package developed for the steady-state TMB model considers axial dispersion flow for the bulk fluid phase and the linear driving force (LDF) approximation is used to describe the intraparticle mass transfer rate. The model can handle any kind of adsorption isotherm. Model equations for the steady-state TMB model are summarized in *table I* with the boundary conditions, as well as with the necessary mass balances at the nodes between each section. The resulting model parameters are:

$(1 - \varepsilon) / \varepsilon$, the ratio between solid and fluid volumes;

$\gamma_j = v_j / u_s$, the ratio between fluid and solid velocities;

$Pe_j = v_j L_j / D_{Lj}$, Peclet number;

$\alpha_j = kL_j / u_s$, number of mass transfer units.

Model equations were numerically solved by using the COLNEW software [6] which implements a finite-element collocation technique for mixed-order systems of linear or nonlinear boundary-value ordinary differential equations.

3. Prediction of the Separation Regions and Process Performance

The SMB performance is characterized by four process parameters: purity, recovery, solvent consumption and adsorbent productivity. For the case of a binary separation in which the less retained species A is recovered in the raffinate and the more retained component B is recovered in the extract, process performance parameters are defined in *table II*.

The effect of the operating and model parameters on the SMB performance is analyzed for the case of the separation of bi-naphthol enantiomers. The purified bi-naphthol enantiomers are used as chiral building blocks in asymmetric synthesis. The enantioseparation can be carried out using 3,5-dinitrobenzoyl phenylglycine bonded to silica gel as stationary phase and heptane-isopropanol (72:28) as eluent [7,8]. A bi-Langmuir model is proposed for adsorption equilibrium isotherms and were measured by the NOVASEP group (personal communication):

$$q_A^* = \frac{2.69c_A}{1 + 0.0336c_A + 0.0466c_B} + \frac{0.10c_A}{1 + c_A + 3c_B} \quad (1a)$$

$$q_B^* = \frac{3.73c_B}{1 + 0.0336c_A + 0.0466c_B} + \frac{0.30c_B}{1 + c_A + 3c_B} \quad (1b)$$

Table I. Model equations for the steady-state TMB model.

Mass balance in a volume element of the bed j :

$$D_{Lj} \frac{d^2 c_{ij}}{dz^2} - v_j \frac{dc_{ij}}{dz} - \frac{(1-\epsilon)}{\epsilon} k(q_{ij}^* - q_{ij}) = 0 \quad (2)$$

Mass balance in the particle:

$$u_s \frac{dq_{ij}}{dz} + k(q_{ij}^* - q_{ij}) = 0 \quad (3)$$

Boundary conditions for section j :

$$z = 0 : \quad c_{ij} - \frac{D_{Lj}}{v_j} \frac{dc_{ij}}{dz} = c_{ij,0} \quad (4)$$

where $c_{ij,0}$ is the inlet concentration of species i in section j .

$$z = L_j : \quad c_{ij} = c_{ij+1,0} \quad \text{for extract and raffinate nodes} \quad (5a)$$

$$c_{ij} = \frac{v_I}{v_{IV}} c_{ij+1,0} \quad \text{for the eluent node} \quad (5b)$$

$$c_{ij} = \frac{v_{III}}{v_{II}} c_{ij+1,0} - \frac{v_F}{v_{II}} c_i^F \quad \text{for the feed node} \quad (5c)$$

$$\text{and} \quad q_{ij} = q_{ij+1,0} \quad (6)$$

Global balances:

$$v_I = v_{IV} + v_E \quad \text{eluent node} \quad (7a)$$

$$v_{II} = v_I - v_X \quad \text{extract node} \quad (7b)$$

$$v_{III} = v_{II} + v_F \quad \text{feed node} \quad (7c)$$

$$v_{IV} = v_{III} - v_R \quad \text{raffinate node} \quad (7d)$$

Multicomponent adsorption equilibrium isotherm:

$$q_{Aj}^* = f_A(c_{Aj}, c_{Bj}) \quad \text{and} \quad q_{Bj}^* = f_B(c_{Aj}, c_{Bj}) \quad (8)$$

where $i = A, B$ refers to the species in the mixture, and $j = I, II, III, IV$ is the section number.

Table II. SMB performance criteria.

Performance Parameter	Extract	Raffinate
Purity (%)	$PUX = 100C_B^X / (C_A^X + C_B^X)$	$PUR = 100C_A^R / (C_A^R + C_B^R)$
Recovery (%)	$RCX = 100Q_X C_B^X / Q_F C_B^F$	$RCR = 100Q_R C_A^R / Q_F C_A^F$
Solvent Consumption (l/g)	$SC = (Q_E + Q_F) / [Q_F (C_A^F + C_B^F)]$	
Productivity (g/day l of bed)	$PR = Q_F (C_A^F + C_B^F) / V_T$	

The conditions for enantiomers separation can be defined in terms of the γ_j model parameters, which are directly related with the TMB operating variables (fluid and solid velocities in the four sections of the TMB unit). From the four γ_j values, those related to sections II and III are the ones that play the key role in the separation performance. Taking into account this consideration, a region of complete separation in a γ_{III} - γ_{II} plane can be defined. The conditions for complete enantiomer separation were analyzed in the frame of the equilibrium theory, where mass transfer resistances and axial dispersion are neglected, by Morbidelli and co-workers [9,10].

If mass transfer resistance is important, we may not obtain a region for complete separation (100% pure enantiomers). In these cases, a purity criteria can be proposed and the region for separation (where both enantiomers purities are at least equal to the proposed purity criteria) can be evaluated using the steady-state TMB model described before.

A study of the influence of the mass transfer resistance in the separation region is carry out. The γ_{III} - γ_{II} plots were built keeping constant the recycling (flow rate in section *IV*) and solid flow rates, and so γ_{IV} . The total inlet or outlet flow rates were kept constant in all simulations and equal to 25.09 ml/min. Other operating conditions and model parameters are summarized in *table III*. A recycling flow rate of 27.95 ml/min in the TMB corresponds to a recycling flow rate of 35.38 ml/min in the SMB; a TMB solid flow rate of 11.15 ml/min corresponds to a switch time interval of 3 min in the SMB unit [5].

Figures 1 and 2 show the γ_{III} - γ_{II} plots obtained for a mass transfer coefficient of $k=0.5 \text{ s}^{-1}$ ($\alpha=180$) (open squares) and $k=0.1 \text{ s}^{-1}$ ($\alpha=36$) (closed squares) using a 95% and 99% purity criteria, respectively. Inside the region delimited by the square points obtained numerically, both the raffinate and the extract are at least 95% (*figure 1*) or 99% (*figure 2*) pure. It can be concluded that mass transfer resistance reduces the region of separation of both enantiomers and that the region obtained for a lower mass transfer coefficient ($k=0.1 \text{ s}^{-1}$) lies inside the region obtained when mass transfer resistance is not so important ($k=0.5 \text{ s}^{-1}$). Hence, the choice of the best operating conditions must take into account the mass transfer resistance phenomenon.

Table III. Operating conditions and model parameters for the γ_{III} - γ_{II} plot.

TMB operation conditions		Model parameters	
Feed concentration:	2.9 g/l each	Solid/fluid volumes:	$(1-\epsilon)/\epsilon = 1.5$
Solid flow rate:	11.15 ml/min	Peclet number:	$Pe = 2000$
Recycling flow rate:	27.95 ml/min	Ratio between fluid and solid velocities	
Column diameter:	2.6 cm	in zone <i>IV</i> :	$\gamma_{IV} = 3.76$
Zone length:	21.0 cm		

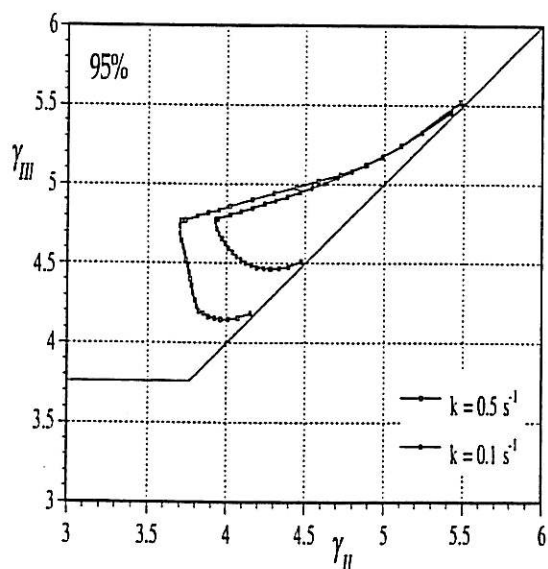


Figure 1. Influence of the mass transfer resistance on the separation region: γ_{III} - γ_{II} plot for a 95% purity criteria.

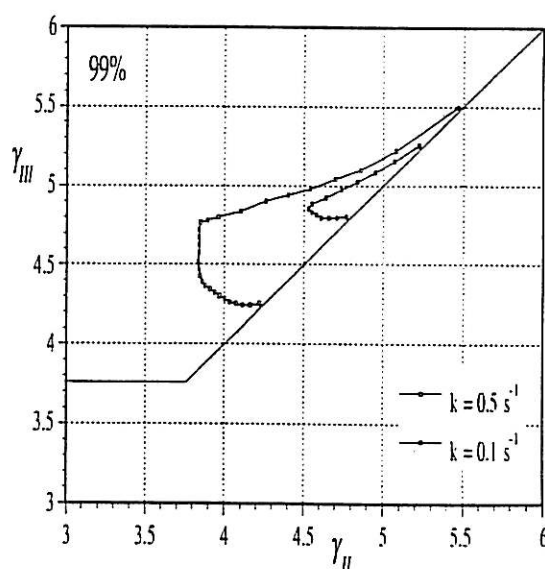


Figure 2. Influence of the mass transfer resistance on the separation region: γ_{III} - γ_{II} plot for a 99% purity criteria.

For practical purposes, it is desirable to work with variables directly related with the SMB unit. Instead of presenting the separation region in a $\gamma_{III}-\gamma_{II}$ plot, we can report the same information in a Q_X versus Q_F plot. Equations 9 and 10 present the conversion rules between the TMB operating conditions and feed and extract flow rates. The eluent flow rate will be $25.09-Q_F$ and the raffinate flow rate $25.09-Q_X$. Figure 3 presents the separation region for $k=0.1 \text{ s}^{-1}$ following a 95% purity criteria. In the region limited by the closed squares both raffinate and extract purities are at least 95%. Open squares in figure 3 show the path of equal purities for extract and raffinate. Since the objective of the SMB operation is to obtain the two enantiomers, the path of equal purities is the optimum trajectory that must be followed [11].

$$Q_F = \frac{\varepsilon}{1-\varepsilon}(\gamma_{III} - \gamma_{II})Q_s \quad (9)$$

$$Q_X = \frac{\varepsilon}{1-\varepsilon}(\gamma_I - \gamma_{II})Q_s \quad (10)$$

Figure 4 presents the optimum purities (and recoveries) that can be expected for a given feed flow rate. It should be pointed out that, when racemic mixtures are fed into a SMB unit, if extract and raffinate purities are equal, recoveries of both extract and raffinate are also equal and with the same value of the purity obtained. Figure 5 presents the solvent consumption and adsorbent productivity obtained as a function of the feed flow rate. Of course, this figure should not be used without looking for figure 4: the increase of the feed flow rate lead to better solvent consumption and productivity performances, but it is followed by a decrease in both purities and recoveries of extract and raffinate. Furthermore, the higher the feed flow rate, the smaller the range of extract flow rates that lead to both enantiomer separation. This means that the process robustness also decrease with the increase of the feed flow rate.

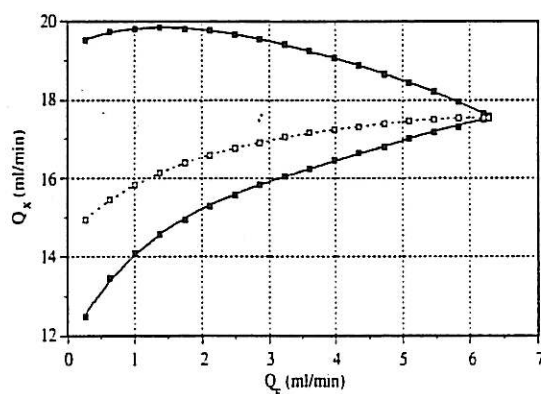


Figure 3. Separation region in a Q_X versus Q_F plot (closed squares). Open squares present the path of equal raffinate and extract purities. (mass transfer coefficient, $k=0.1 \text{ s}^{-1}$; purity criteria: 95%)

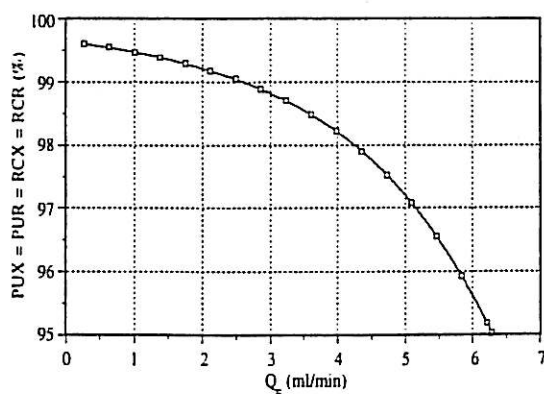


Figure 4. Optimum purities and recoveries as a function of the feed flow rate.

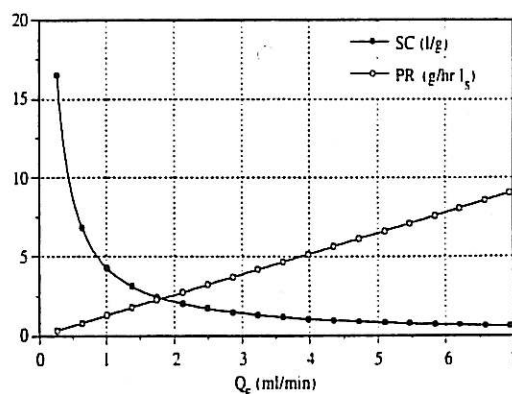


Figure 5. Solvent consumption and adsorbent productivity as a function of the feed flow rate.

4. Operation of a SMB pilot unit

The operation of the SMB pilot for the bi-naphthol enantiomers purification was carried out using a 8-column configuration (2 per section). Columns are made of 3,5-dinitrobenzoyl phenylglycine bonded to silica gel (*Merck, Darmstadt, Germany*). Each column is 2.6 cm ID x 10.5 cm long. Silica particles have diameter in the range 25 to 40 μm . The eluent used was a 72/28 (v/v) heptane/isopropanol mixture. Operation temperature was fixed at 25 C.

Four runs were carried out to study the effect of the switch time interval on the SMB process performance. *Table IV* presents the experimental conditions for the SMB pilot. The internal profiles were measured using the 6-port valve of the *Licosep* SMB pilot to withdraw samples from the system. The samples were collected at each half-time period and after 40 full cycles of continuous operation. The experimental performance parameters were determined by analysis of the extract and raffinate samples collected during the whole cycle 40 (cyclic steady-state).

The experimental performance parameters obtained are shown in *table V*. For a switch time interval of 2.80 minutes purities and recoveries higher than 95% were obtained for both extract and raffinate.

Figures 6 and 7 show the experimental purities obtained in the four runs as well as the model predictions for different values of mass transfer coefficient. A good agreement between model and experimental results are obtained for $k=0.1 \text{ s}^{-1}$.

Table IV. Experimental SMB operating conditions for the bi-naphthol system.

Feed concentration, g/l each:	2.9	Switch time interval, min:	
Recycling flow-rate, ml/min:	35.38	Run A: 2.55	
Eluent flow-rate, ml/min:	21.45	Run B: 2.75	
Extract flow-rate, ml/min:	16.00	Run C: 2.80	
Feed flow-rate, ml/min:	3.64	Run D: 3.05	
Raffinate flow-rate, ml/min:	9.09		

Table V. Experimental performance parameters for the four runs.

Run	PUX	PUR	RCX	RCR	SC	PR
A	74.0	93.8	96.0	66.6		
B	93.0	96.2	97.3	91.6	1.19	68.2
C	95.6	95.4	95.0	96.1		
D	91.5	70.9	61.5	94.7		

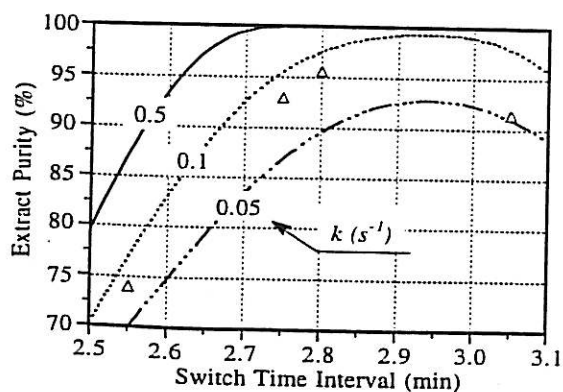


Figure 6. Extract purity: Comparison between experimental and model predictions.

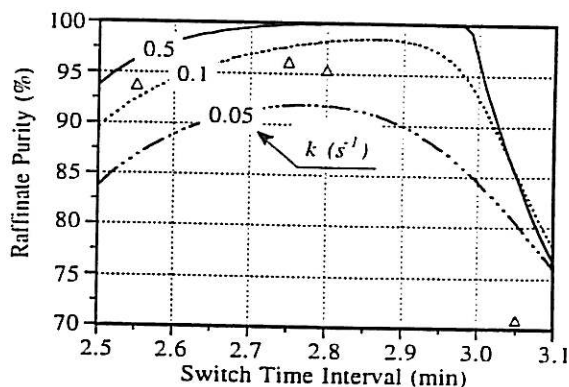


Figure 7. Raffinate purity: Comparison between experimental and model predictions.

Figure 8 shows the SMB experimental internal concentration profiles for run B at cyclic steady-state. Simulated results are also displayed using $k = 0.1 \text{ s}^{-1}$ (symbols are experimental results, lines for model simulation). The agreement between model and experimental results is reasonable except for the concentration of the more retained component B in the column before the feed inlet. This discrepancy may be due to the fact that the sample is collected at the half-time period; the composition at that time can be different from the average composition in the whole rotation period. It can also be related with an inaccurate description of the binary adsorption equilibrium.

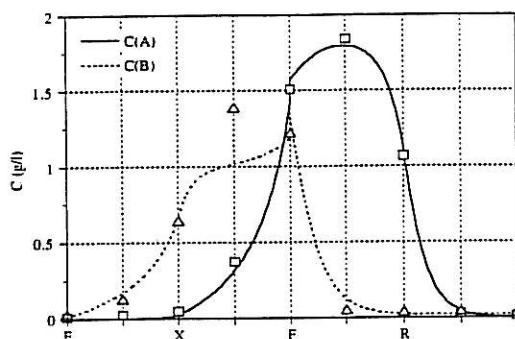


Figure 8. Comparison between experimental (points taken at half time period in the cyclic steady-state, SMB operation) and simulated (steady-state TMB operation) internal profiles.

5. Conclusions

The main problem of the SMB operation consists in choosing the better solid (switch time interval) and liquid flow rates. A model for predicting the cyclic steady-state behaviour of a SMB chromatographic system is presented using the equivalent true moving bed approach. The simulation package considers non-linear competitive adsorption isotherms, axial dispersion and the linear driving force approximation is used to describe the intraparticle mass transfer rate.

The SMB/TMB package is an important learning and training tool used to predict the effect of operating variables on the process performance, and so the choice of these best conditions for the SMB operation. The regions for enantiomer separation can be numerically predicted, considering dispersion and mass transfer resistances phenomena. The mass transfer resistance phenomenon affects the separation region of both enantiomers.

The set of figures 3, 4 and 5 provide a practical tool for choosing the better SMB operating conditions as a function of the feed flow rate. The optimum is found following the path of equal extract and raffinate purities and will result from a trade-off between solvent consumption and adsorbent productivity, purity and recovery requirements, and system robustness.

The separation of bi-naphthol enantiomers was carried out in a SMB pilot unit *Licosep 12-26*. Purities and recoveries higher than 95% were obtained for both extract and raffinate, using a 450 ml inventory of stationary phase. A productivity of 68.2 grams of racemic mixture processed per day and per liter of bed was obtained. The solvent consumption was 0.19 liters of mobile phase per gram of racemic mixture processed. The predictions of process performance and steady-state internal concentration profiles were carried out with reasonable agreement with experimental results.

6. Nomenclature

c	fluid phase concentration		
D_L	axial dispersion coefficient		
k	mass transfer coefficient		
L_j	length of section j		
Pe	Peclet number		
Q	volumetric liquid flow rate		
Q_s	solid flow rate		
q	average adsorbed phase concentration		
q^*	adsorbed concentration in equilibrium with c		
u_s	solid velocity		
V_T	volume of the adsorbent bed		
v_j	interstitial fluid velocity		
z	axial coordinate		
		<i>Greek symbols:</i>	
		α_j	number of mass transfer units
		ϵ	bed porosity
		γ	ratio between fluid and solid velocities
			<i>Subscripts and superscripts:</i>
		A	less retained component
		B	more retained component
		E	eluent
		F	feed
		R	raffinate
		X	extract

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