Theoretical Study of Recycling in Preparative Chromatography

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Using the equilibrium-dispersive model of chromatography, we have investigated recycling as a means to improve the recovery yields and possibly the production rates of chromatographic separations. When compared with the optimal values obtained for the conventional single-cycle regime, our results prove the potential for recycling in preparative chromatography. The analysis performed for the separation of two binary mixtures demonstrates that recycling not only improves the recovery yield but can increase the production rate under certain conditions. Different possibilities of collecting sufficiently separated fractions during recycling are compared. The mathematical model developed can be used effectively for designing optimal recycling strategies in preparative liquid chromatography.

Introduction

The popularity of preparative liquid chromatography as a separation technique for the production of high-purity drugs and biomolecules is increasing rapidly. When appropriate stationary phases ($\alpha > 1.5$ and Langmuirian isotherms for the two components with close values of the column saturation capacity) are available, the process can be performed in the conventional, single-run elution regime used in analytical applications of chromatography. However, difficulties in separations, when separation factors are below 1.5, are encountered frequently. In such cases, the production rate achieved is low, and the exploration of less classical procedures becomes attractive. The important problem of the separation and/or purification of optical isomers is a case in point. Although values of the separation factor of enantiomers well in excess of 10 have been reported (Pirkle and Pochapsky, 1989), there are many instances where the chiral stationary phases available for these separations give low separation factors.

Several concepts designed to overcome the insufficient separation afforded by the conventional methods have been proposed by Wankat (1986). The subsequent reinjection of insufficiently purified fractions was studied by Crary et al. (1989). Bailly and Tondeur (1982) have applied this principle in combination with the injection of a certain amount of fresh feed in each cycle. Several techniques of countercurrent and

crosscurrent chromatography were compared by Barker and Ganetsos (1989). Ruthven and Ching (1989) have reviewed the simulated countercurrent or moving-bed principle. This sophisticated technique was applied recently by Fish et al. (1988) and Ray et al. (1990) to study equilibrium reactions with subsequent separation of their products.

When a separation cannot be performed in a single run under optimal conditions with a sufficiently high production rate, the most simple approach is still to increase the column length to enhance the efficiency of the column. Due to increasing inlet pressure requirements, there exists a limit to the number of theoretical plates that can be achieved. Further, for large-scale preparative applications, a given column must often be used, and an increase in the column length is not always possible. Continuous recycling offers an easy way to simulate a longer column and has the advantage that no increase in the column inlet pressure is required. A serious limitation is set, however, by the requirement that dead volumes in the recycle line should not cause significant additional band broadening.

The simplest closed-loop recycling consists of connecting the detector outlet with the pump inlet (Bombaugh et al., 1969; Biesenberger et al., 1971). Since the pump contributes much more to band spreading than do connecting tubes and valves, Duvdevani et al. (1971) applied another method, using two nearly identical columns. In this so-called "alternate pumping recycling," the sample passes alternately through two columns and the pump is not included in the circuit. This method has

the drawback that each of the two columns must be half as long as the column used in the single-loop approach, which reduces in proportion the acceptable spread of the sample in the column.

A general problem connected with recycling is the fact that peaks can be cycled only until they begin to overlap. To avoid that the first peak of a cycle reaches the last peak of the former cycle, it is advantageous to collect in each cycle the fractions of the sample that already fulfill purity requirements (peak shaving).

Several successful applications of closed-loop recycling and alternate pumping have been reported in the field of gel permeation chromatography (Bombaugh et al., 1969, 1970; Bombaugh, 1970; Duvdevani et al., 1971; Nakamura et al., 1973; Lesec et al., 1974; Lesec and Quivoron, 1976) for separations of enantiomers (Henry, 1974; Schlögl and Widhalm, 1984; Werner, 1989) and for the isolation of vitamins (Letter, 1992).

Hitherto, no detailed theoretical studies concerning the recycling regimes of preparative chromatography and their optimization were undertaken. Martin et al. (1976) have studied recycling exclusively under analytical (linear) conditions. They derived theoretical expressions to determine the limit cycle number beyond which the effect of remixing spoils the achieved separation. As peak shaving is not applicable in analysis, it was not considered in that work.

To the best of our knowledge, no quantitative comparison of the applicability of recycling chromatography with an optimized conventional single-cycle elution approach is available in the field of preparative chromatography. The justification for using recycling is that it will always improve the recovery yield. The production rate, however, is another very important characteristic of an efficient process (Golshan-Shirazi and Guiochon, 1991). The consequences of recycling on the production rate are not obvious, and a valid comparison between the two approaches can be made only on the basis of optimized methods.

Recently, Felinger and Guiochon (1992) published a theoretical study of optimizing experimental conditions for maximum production rate with a single-cycle system. In this work, influences of the retention factor of the first component and of the relative retention of the components of a binary mixture on the optimal conditions were determined.

Our objective is to analyze, on the basis of the equilibrium-dispersive model, different regimes of recycling in high-performance liquid chromatography. The analysis is performed using the same examples as Felinger and Guiochon (1992), and a quantitative comparison is made of the results obtained with the optimal results of the conventional single-cycle regime.

Techniques for Recycling Chromatography

Figure 1 shows the simplest recycling technique, the closed-loop approach. To achieve good results, it is essential to choose an appropriate pump minimizing the remixing effects. The pump having the smallest stroke volume for the required flow rate will give the best results. A further advantage of recycling is that no fresh solvent is necessary during the periods of recycling. This fact can have considerable economic consequences, as the cost of the mobile phase is often the largest single contribution to the total purification costs.

Figure 2 illustrates the alternate pumping principle proposed
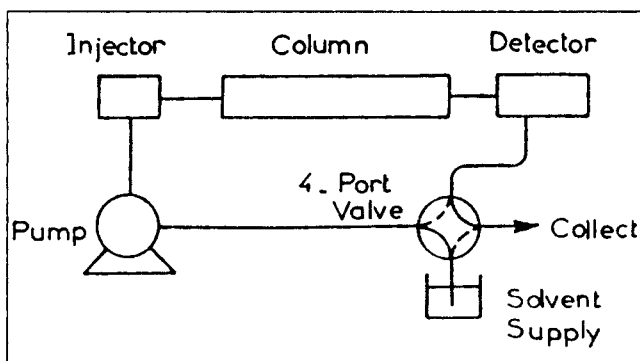

Figure 1. Closed-loop recycling apparatus.

by Duvdevani et al. (1971). When the sample has left one of the columns and entered the second one, the six-port valve is switched so that the positions of the two columns with respect to the direction of flow are exchanged. The main advantage of this recycling regime is that the sample does not have to pass through the pump, and remixing is limited to the contributions of the connecting tubes and the valve. This principle does not offer the possibility of saving solvent as does the closed-loop approach.

Common to both techniques of recycling is that they simulate a longer column. Neglecting all mixing effects in the connecting lines, the closed-loop approach and the alternate pumping principle can be treated as nearly identical as when the two columns used in the latter regime together have the same length as the column of the closed-loop approach. In this case, a cycle of the alternate pumping principle is connected with two switches of the valve to transport the sample through both columns. The only difference is that in the alternate pumping method, the sample cannot spread beyond the volume of one of the two columns.

If the composition at the column outlet can be recorded continuously, the fractions of the sample which are sufficiently
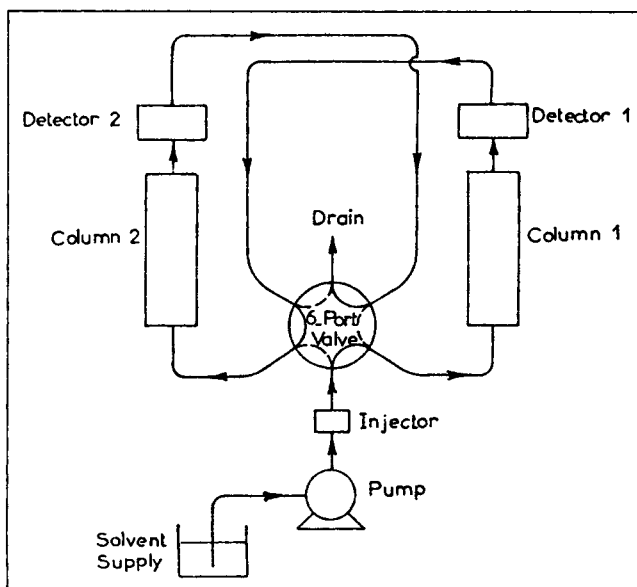

Figure 2. Alternate pumping recycling apparatus.

separated can be collected, so only part of the sample, not the whole, needs to be recycled. As demonstrated below for a binary system, this method improves the production rate. However, to fully exploit the whole potential of this peak shaving technique for practical applications, the availability of fast on-line analysis is required. The concentrations of the feed components at the column outlet have to be measured and integrated in connection with a mass balance of the sample to determine the cut points between recycling and fraction collection. This on-line analysis is easy when the feed components have different UV-spectra or other physico-chemical properties (such as polarimetry or circular dichroism for optical isomers, Zukowski et al., 1992). Fast micro-HPLC might be used for some systems, but the requirements regarding the time constant of the analysis are severe.

Mathematical Model

In many recent investigations, the equilibrium-dispersive model has been proven to be a reliable tool to account for experimental chromatograms (Katti and Guiochon, 1991; Katti et al., 1992). On the basis of this model, several attempts were undertaken to optimize chromatographic separations for preparative purposes (Golshan-Shirazi and Guiochon, 1991; Katti et al., 1991; Felinger and Guiochon, 1992). The most important objective functions for this optimization are the production rate of either one of the feed components and its recovery yield. This model and these earlier optimization approaches will be used in this work.

Equilibrium-dispersive model

In the mass balance of the equilibrium-dispersive model, the effects of the axial dispersion and the possible mass-transfer resistance are lumped in an apparent dispersion coefficient, D_{ap}.

$$\frac{\partial C_i}{\partial t} + F\frac{\partial q_i}{\partial t} + u\frac{\partial C_i}{\partial x} = D_{ap_i}\frac{\partial^2 C_i}{\partial x^2} \quad i=1, N \tag{1}$$

In this equation, the concentrations in the stationary and mobile phases q and C are related through the adsorption isotherm:

$$q_i = q_i(C_1, C_2, ..., C_N) \quad i=1, N \tag{2}$$

Due to the fact that both phases are assumed to be in equilibrium, the phase ratio $F = (1 - \epsilon_T)/\epsilon_T$ is based on the total porosity, ϵ_T, representing the liquid fraction in the interstitial space of the column and inside the pores of the stationary phase. The parameter u is the interstitial mobile-phase velocity.

Because of the high efficiency of HPLC columns, the boundary conditions needed to solve Eq. 1 can be simplified. Neglecting the effect of backmixing at the column inlet, the simple condition:

$$C_i(t, x=0) = C_{i_E}(t) \quad i=1, N \tag{3}$$

can be used. Equation 3 is used to model recycling by setting the concentrations at column inlet equal to the outlet concentrations. In the case of a single-cycle system, the functions

$c_{iE}(t)$ are usually rectangular profiles, representing the injection of the sample. This holds only for the period of the initial injection in recycling regimes. As quantified below, these functions become later more complicated and depend on the position of the valves performing the switching between elution and recycling.

The second boundary condition and the initial condition necessary to solve Eq. 1 are:

$$\frac{\partial C_i}{\partial x}\bigg|_{x=L} = 0 \quad i=1, N \tag{4}$$

and

$$C_i(t=0, x) = 0 \quad i=1, N \tag{5}$$

Because of the nonlinear character of Eq. 2, numerical methods are needed to solve the system of Eqs. 1 to 5. The finite difference method proposed by Rouchon et al. (1987) and analyzed by Czok and Guiochon (1990) was used in this work.

Optimization of the single-cycle regime

Felinger and Guiochon (1992) used the equilibrium-dispersive model to optimize the production rate in overloaded elution for the separation of a binary mixture. They used the competitive Langmuir isotherm model to account for the adsorption equilibrium:

$$q_i = \frac{a_i C_i}{1 + b_1 C_1 + b_2 C_2} \quad i=1, N \tag{6}$$

and the Knox equation (Knox, 1977) to express the dependence of D_{ap} on the linear velocity u:

$$h = \frac{2}{\nu} + \nu^{1/3} + \frac{\nu}{10} \tag{7}$$

where $h = L/(N_p d_p)$ is the reduced column plate height and $\nu = (u d_p)/D_m$ is the particle Peclet number or reduced velocity; L is the column length, N_p the number of theoretical plates related to D_{ap}, $D_{ap} = (uL)/(2N_p)$, d_p the particle diameter, u the mobile-phase velocity, and D_m the diffusion coefficient of a component in the mobile phase. The parameters used by Felinger and Guiochon (1992) are given in Table 1.

The production rate to be optimized is defined as:

$$R_i = \frac{m_i}{(t_2 - t_1)A_c\epsilon_T} \tag{8}$$

where $t_2 - t_1$ is the cycle time, that is, the time between two consecutive injections. This cycle time is determined from the time, t_1, when the concentration of the first eluted component exceeds a given threshold C_{min}, and the time, t_2, when the concentration of the second component drops below this same threshold.

The recovered amount of the component 1, m_1, was determined by integration of the chromatograms between t_1 and the cut time t_{c1}, and the recovered amount m_2 by integration between the cut time t_{c2} and t_2. Both cut times are calculated

Table 1. Parameters of the Optimization Study of Felinger and Guiochon (1992)

Parameters
Column and System
$L = 25$ cm
$d = 0.46$ cm
$d_p = 20 \, \mu m$
$\epsilon_T = 0.8$
$F = 0.25$
$D_m = 10^{-5}$ cm^2/s $= D_{m1} = D_{m2}$
$v_{inj} = 0.15$ mL
Isotherm
$a_1 =$ optimized (as retention factor $k_1' = Fa_1$)
$a_2 = \alpha a_1 (\alpha$ given)
$q_{si} = a_i/b_i = 1,300$ g/L, $i = 1, 2$
Optimization
$Pu_1 = Pu_2 = 0.99$
$c_{min} = 10^{-6}$ g/L

Table 2. Optimal Values of k_1', ν and L_f and Corresponding Maximal Production Rates R_i and Recovery Yields Y_i Determined by Felinger and Guiochon (1992) for $\alpha = 1.2$

C_{01}/C_{02}	Opt. Comp. i	k_1'	ν	L_f	R_i (mg/cm$^2 \cdot$s)	Y_i
3:1	1	1.5	124	0.0684	2.371	0.370
		1.6*	102*	0.0414*	1.970*	0.600*
		2.3*	62*	0.0221*	0.909*	0.900*
3:1	2	1.7	89	0.0408	0.278	0.275
		2.0*	69*	0.0217*	0.241*	0.600*
		2.7*	45*	0.0135*	0.137*	0.900*
1:3	1	1.8	55	0.0611	0.413	0.487
		1.9*	52*	0.0479*	0.401*	0.600*
		2.4*	39*	0.0290*	0.252*	0.900*
1:3	2	1.5	171	0.0553	1.725	0.263
		1.7*	121*	0.0279*	1.547*	0.600*
		1.9*	64*	0.0215*	1.064*	0.900*

* Optimization-included constraint with respect to recovery yield. These parameters are only given for comparison. The values for k_1', ν, and L_f were not applied in simulations of cyclic regimes.

from the integrated chromatograms using the times when the required purities are achieved (Katti et al., 1991; Felinger and Guiochon, 1992).

For a given separation factor, $\alpha = a2/a1$, a given composition of the sample, c_{01}/c_{02}, and a required purity of the products, $Pu_i = m_i/(m_1 + m_2)$, a Simplex method supplies the optimal values of the retention factor of the first component k_1', the reduced velocity ν, and the loading factor L_f, for maximum production rate of either the first or second component (Felinger and Guiochon, 1992). The retention factor can be adjusted in chromatographic separations by appropriate changes of the solvent composition. With respect to the reduced velocity, a maximum value of 400, which corresponds to standard correlations to a pressure drop of about 125 bar, was set as a constraint. The loading factor is related to the amount injected and the column saturation capacity ($q_s = a_i/b_i$) as:

$$L_f = \frac{(C_{01} + C_{02})v_{inj}}{V_c \epsilon_T q_s} \quad (9)$$

The method described gives the maximum production rate with a given column. The column length and the particle size may also be optimized for maximum production rate. In some cases, the optimization of the production rate was performed considering constraints with respect to the recovery yield, $Y_i = m_i/m_{iinj}$. Convergence of the Simplex method was demonstrated by showing that the response surface behaves well.

Table 2 shows the results of Felinger and Guiochon (1992) for the single-cycle regime that are relevant for comparisons with the recycling techniques discussed below. In Figures 3 and 4, we show the chromatograms calculated in the single-cycle regime, under the conditions reported by Felinger and Guiochon (1992), for the two sample compositions studied, $C_{01}/C_{02} = 3:1$ and $C_{01}/C_{02} = 1:3$. In both cases, the production rate for the less concentrated component was optimized. In these figures, the positions of cut points, t_{c1} and t_{c2}, are shown by straight lines, framing the fraction of the samples which is not sufficiently separated.

Boundary conditions and cut points for recycling

In the following, we discuss four different procedures for performing recycling chromatography for the separation of a

binary mixture and compare their results. These four methods differ only in the fraction collection or "peak shaving," which is made during each cycle:

SHA0. No fractions are collected, but the whole sample is recycled for n cycles. Thus, this method is identical to the use of an n-times longer column in the single-cycle regime. SHA0 provides a reference for the assessment of the advantages and/or drawbacks of the other procedures.

SHA1. Only the fraction that contains component 1 at the required degree of purity is collected during each cycle.

SHA2. Only the fraction that contains component 2 at the required degree of purity is collected during each cycle.

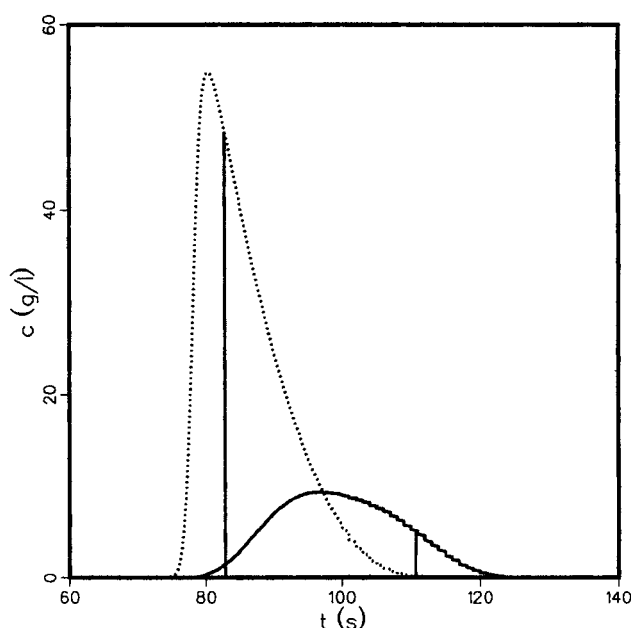*SHA12.* Both of the fractions that contain components 1

Figure 3. Separation of a 3:1 mixture in the single-cycle regime for the parameters allowing a maximum production rate for component 1 (Table 2).
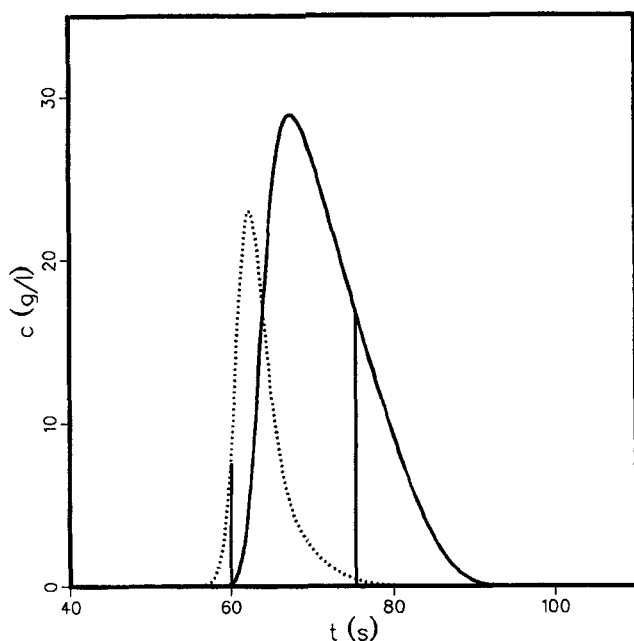
Figure 4. Separation of a 1:3 mixture in the single-cycle regime for the parameters allowing a maximum production rate for component 2 (Table 2).

and 2 at the required degree of purity are collected during each cycle.

If in the alternate pumping regime fractions are collected only at the outlet of the second column, and if we assume that no additional band broadening effects are operating outside the column(s), the following considerations apply to both the closed-loop and alternate pumping regime.

The most critical problem for a mathematical description of recycling is to properly determine the cut points $t_{1,n}$, $t_{c1,n}$, $t_{c2,n}$, and $t_{2,n}$ for each cycle, n. At these times, changes in the flow stream are performed by switching a valve. These changes are represented in the model by corresponding discontinuities of the column inlet boundary condition (Eq. 3), the recycling of the component concentrations eluting from the column being replaced by the injection of pure mobile phase or conversely. The times $t_{1,n}$ and $t_{2,n}$ defining the beginning and end of cycle n are specified with the same threshold concentration $C_{\min}$ as in the single-cycle regime. The time $t_{c1,n}$ when the amount of component 2 in the first fraction just exceeds the value corresponding to the required purity, Pu_1, is easily calculated by integration of both concentration profiles, according to the equation:

$$1 - Pu_1 = \frac{\displaystyle\int_{t_{1,n}}^{t_{c1,n}} C_2(t, L)dt}{\displaystyle\int_{t_{1,n}}^{t_{c1,n}} C_1(t, L)dt + \int_{t_{1,n}}^{t_{c1,n}} C_2(t, L)dt} \quad (10)$$

It is more difficult to determine the time $t_{c2,n}$, since an equation similar to Eq. 10, written for the time interval during which the second component is enriched, requires an integration in the region of the chromatogram still to be eluted.

According to mass-balance considerations, however, the amounts of the two components to be eluted during one cycle are the differences between the injected amounts, $C_{0i} t_p$, and the amounts possibly taken out of the system in earlier cycles, I_{iprev} (Eq. 12), plus the amounts already eluted in the present cycle, I_{iact} (Eq. 13). To satisfy the mass balance in Eq. 12, the low concentrated fractions eluting between two cycles (between $t_{2,k-1}$ and $t_{1,k}$) must also be considered. These dilute fractions should not be recycled. Hence, the cutting time in cycle n, $t_{c2,n}$, can be calculated by solving the following Eq. 11. The fraction of the sample eluting after this time, $t_{c2,n}$, contains the second component with the required purity Pu_2.

$$1 - Pu_2 = \frac{C_{o1} t_p - I_{1prev} - I_{1act}}{C_{o1} t_p - I_{1prev} - I_{1act} + C_{o2} t_p - I_{2prev} - I_{2act}} \quad (11)$$

with

$$I_{iprev} = \sum_{k=1}^{n-1}\left[\int_{t_{2,k-1}}^{t_{1,k}} C_i(t, L)dt \right.$$
$$\left. + F_1\int_{t_{1,k}}^{t_{c1,k}} C_i(t, L)dt + F_2\int_{t_{c2,k}}^{t_{2,k}} C_i(t, L)dt\right] \quad (12)$$

$$I_{iact} = \int_{t_{2,n-1}}^{t_{c2,n}} C_i(t, L)dt \quad (13)$$

In Eqs. 12 and 13, $i = 1$, 2 and $t_{2,0} = 0$.

In Eq. 11, the differences $C_{0i} t_p - I_{iprev}$ represent the amounts recycled during the cycle $n-1$, and which have to be eluted during the cycle n. It should be noted that a slight inaccuracy arises in the determination of $t_{c2,n}$ using Eq. 11. It is due to the fact that the small amount of sample that elutes after the time $t_{2,n}$ when the concentration C_2 drops below $C_{\min}$ is not taken into account.

Finally, in order to solve Eq. 11, we need the values of F_1 and F_2, which depend on the recycling procedure used and are related to the corresponding valve positions. We have: $F_1 = F_2 = 0$ for SHA0; $F_1 = 1$, $F_2 = 0$ for SHA1; $F_1 = 0$, $F_2 = 1$ for SHA2 and $F_1 = F_2 = 1$ for SHA12.

After specifying the times t_1, t_{c1}, t_{c2}, and t_2 for each cycle n, the column inlet boundary condition (Eq. 3) can be expressed as follows. In all four cases, an identical rectangular pulse injection of time width t_p was assumed:

$$C_i(t \leq t_p, x = 0) = C_{0i} \quad (14)$$

We considered only the cases when $t_p < t_{1,1}$, that is, when the complete sample was injected before the first component was eluted. Then, the boundary conditions for the four recycling procedures differ and depend on the cut points. These conditions are summarized in Table 3.

The calculations were stopped if the recovery yields exceeded 99% or if the cycles began to overlap. A possible indication of this latter situation is: $C_2 > C_1$ at $t_{1,n}$.

Results and Discussion

The chromatograms obtained and the production rate achieved with each of the four recycling procedures were cal-

| | E(lute): $C_i(t, x=0)=0$ | | | |
| | R(ecycle): $C_i(t, x=0)=c_i(t, x=L)$ | | | |
Model	$t_{2,n-1} \leq t < t_{1,n}$	$t_{1,n} \leq t < t_{c1,n}$	$t_{c1,n} \leq t < = t_{c2,n}$	$t_{c2,n} < t < t_{2,n}$
SHA0	E	R	R	R
SHA1	E	E	R	R
SHA2	E	R	R	E
SHA12	E	E	R	E

$^*1 < n < n_{max}$ when $n = 1$: $t_{2,0} = 0$. For the last cycle, $n = n_{max}$, only condition E holds.

culated using the model described above, with the sets of parameters determined by Felinger and Guiochon (1992) and summarized in Table 2. We studied the separation of the 1:3 and 3:1 mixtures with $\alpha = 1.2$ and used those previously optimized with single-cycle mode as the experimental conditions, for maximum production rates of either the first or second component, without considering any constraints with respect to the recovery yield (Table 2).

In Figure 5, we show the chromatograms obtained for the first four cycles, when separating the 3:1 mixture. The parameters were optimized for the maximum production rate of the
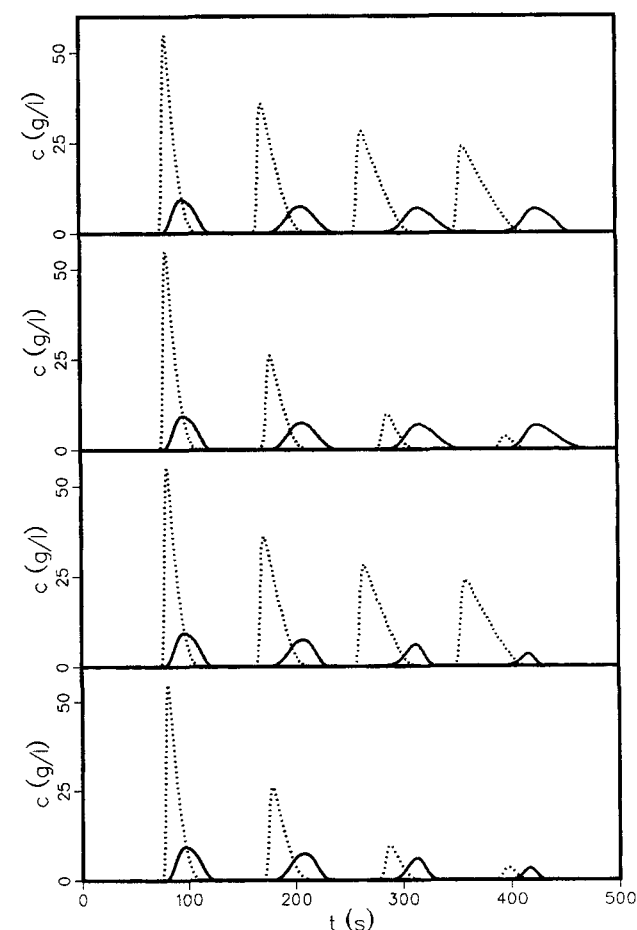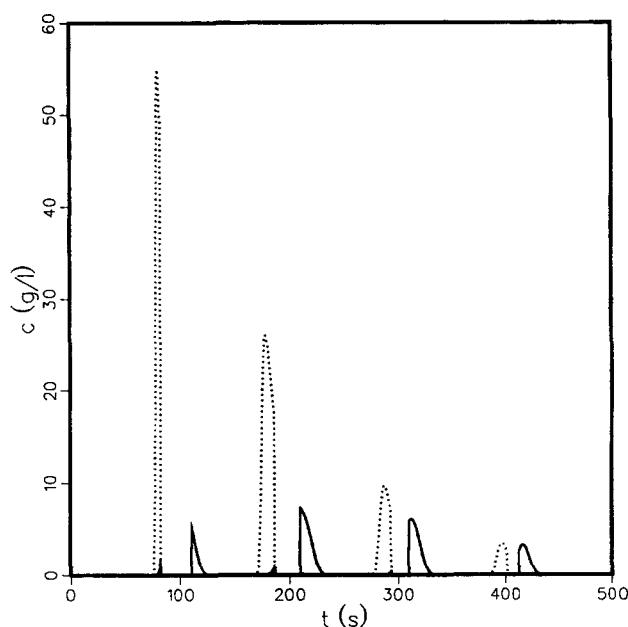

Figure 6. Collected fractions for the 3:1 mixture and the SHA12-model.

more concentrated component. The amount of pure fractions collected during each cycle increases from the top (SHA0) to the bottom (SHA12). If the whole sample is recycled without fraction collection (SHA0), the third and fourth cycle overlaps slightly. This problem is completely avoided by collecting both pure fractions in each cycle (SHA12). In this case, more cycles could obviously have been performed to recover both components completely with a high purity. To illustrate the pure fraction collection procedure over several cycles, Figure 6 shows the concentration profiles of the material collected at the column outlet for the 3:1 mixture with the modal SHA12. The fraction of the sample that is recycled is not shown in the figure. These results correspond to the curves shown at the bottom of Figure 5.

One consequence of collecting fractions is that the actual composition of the sample in the column changes for each cycle. To demonstrate this effect, we use the parameter $M_{21} = (m_{2rec}/m_{2inj})/(m_{1rec}/m_{1inj})$. In Figure 7, the logarithm of this parameter is plotted vs. the cycle number for different cases of recycling the 3:1 (Figure 7a) and 1:3 (Figure 7b) mixtures. When the first component is collected (SHA1), M_{21} increases. The converse hold true when the second component is collected (SHA2). Obviously, M_{21} remains constant in SHA0. No general rules can be given when pure fractions of the two components are collected at the end of each cycle (SHA12), but M_{21} seems to increase when m_{2inj}/m_{1inj} is lower than unity and decrease when m_{2inj}/m_{1inj} is higher than one.

Figures 5 and 6 demonstrate the trivial effect that the recovery yield improves with each new cycle as long as the bands of successive cycles do not overlap and spoil the separation achieved. This fact is further illustrated in Figure 8. Figure 8a shows the cumulated recovery yields after each cycle with the SHA12 procedure. The four curves correspond to the four cases studied (Table 2), and in each case the recovery yield given is for the component for which the parameter allows a maximum production rate in the single-cycle mode. A signif-
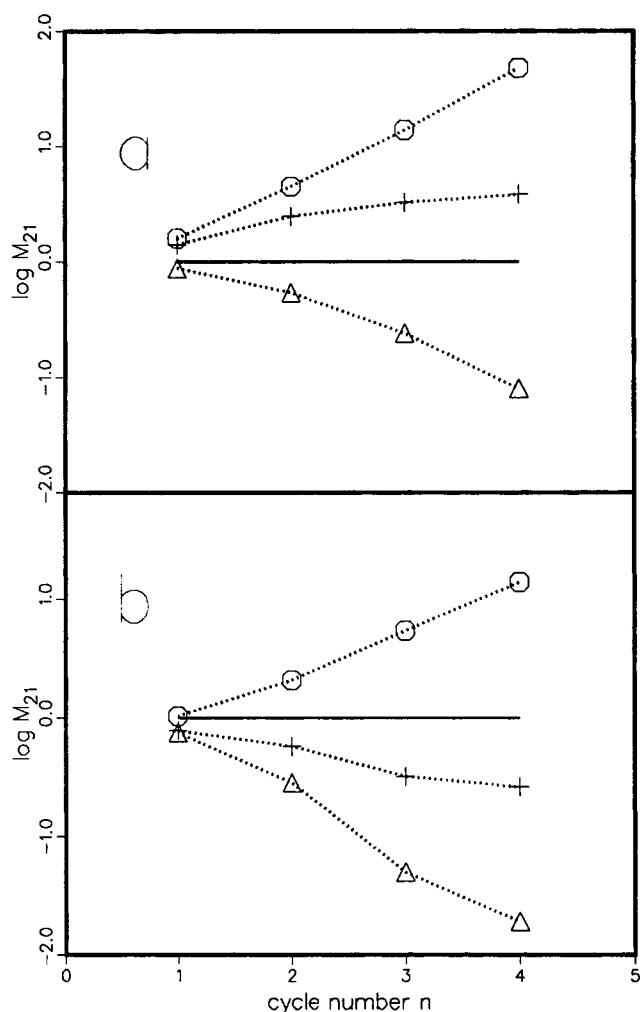

Figure 5. Separation of a 3:1 mixture by recycling. Parameters as in Figure 3.

Models from top to bottom: SHA0, SHA1, SHA2, SHA12.

Figure 7. Change in composition during recycling with fraction collection.

(a) 3:1 mixture, parameters as for Figure 3.
(b) 1:3 mixture, parameters as for Figure 4.
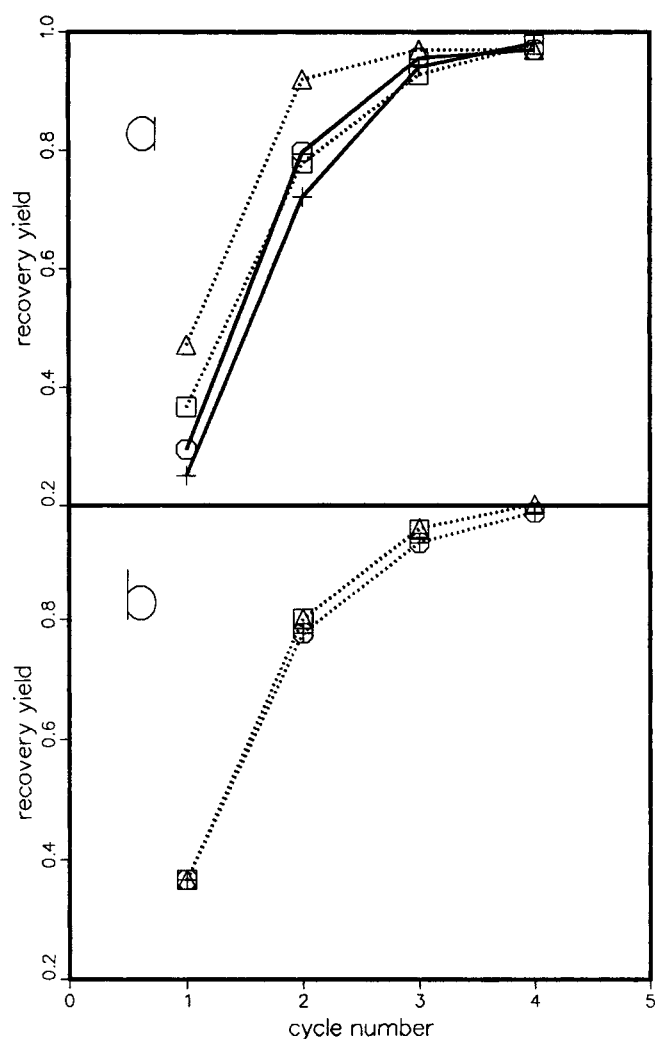
—; SHA0; o, SHA1; ▵, SHA2; +, SHA12.

Figure 8. Recovery yield for component optimized in single-cycle regime in dependence on cycle number.

(a) SHA12 model.

□, 3:1 mixture, optimal parameters for component 1
o, 3:1 mixture, optimal parameters for component 2
▵, 1:3 mixture, optimal parameters for component 1
+, 1:3 mixture, optimal parameters for component 2

(b) 3:1 mixture, optimal parameters for component 1.

□, SHA0; o, SHA1; ▵, SHA2; +, SHA12.

icant increase in the recovery yield is always achieved in the second and third cycles. Complete recovery for both components is nearly achieved at the end of the fourth cycle. Figure 8b shows that the recovery yield increase achieved by recycling is nearly the same with any of the four procedures investigated except for the first procedure (SHA0), with which, due to the overlapping between the third and fourth cycles, no complete recovery can be achieved. The results in Figure 8 are similar for all other cases studied.

Equally important for practical applications is the influence of the number of cycles on the production rate. Of course, the total cycle time or the time between consecutive sample injections will be larger in the recycling mode. In recycling, the cycle time is the difference $t_{2,nmax} - t_{1,1}$. We now investigate the dependence of the production rate on the number of cycles, and the extent to which time spent recycling can be compensated by the increase in the amount produced due to the increase in recovery yield.

Figure 9 shows the dependence of the production rate on

the cycle number for the four cases studied (Table 2) and with the four procedures selected. In most cases, the production rate drops with increasing cycle number. In the cases when the separations were optimized for maximum production rate of the less concentrated component and low reduced velocities, v, were found optimum, three cycles are sufficient for a nearly complete recovery. However, the gain in recovery yield obtained in the last cycle is associated with a considerable decrease in the production rate (Figures 9b and 9d). Figure 9c shows that for the production of the second component of a 1:3 mixture under the conditions studied, a regime consisting of two cycles with or without peak shaving would increase not only the recovery rate but also the production rate.
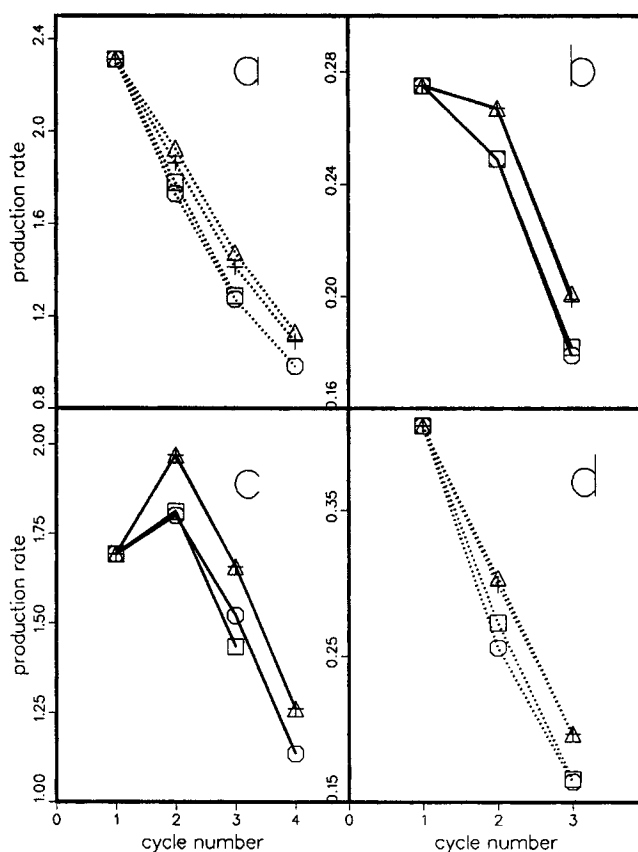
Figure 9. Production rate in dependence on cycle number.

(a) Rate for component 1, 3:1 mixture, optimal parameters for component 1.
(b) Rate for component 2, 3:1 mixture, optimal parameters for component 2.
(c) Rate for component 2, 1:3 mixture, optimal parameters for component 2.
(d) Rate for component 1, 1:3 mixture, optimal parameters for component 1.
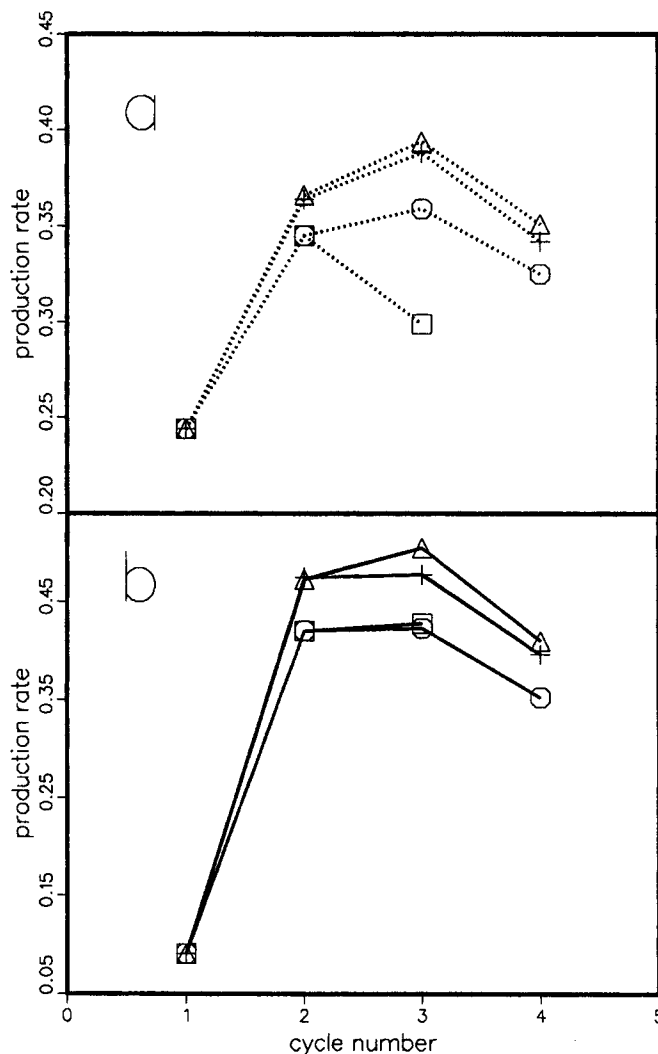
□, SHA0; o, SHA1, △, SHA2; +, SHA12.

Figure 10. Production rate in dependence on cycle number.

(a) Rate for component 2, 3:1 mixture, optimal parameters for component 1.
(b) Rate for component 1, 1:3 mixture, optimal parameters for component 2.

□, SHA0; o, SHA1, △, SHA2; +, SHA12.

The comparison of the results obtained with the different procedures in Figure 9 shows that production rates are the highest in the two cases where the second eluted component is collected in each cycle (SHA2 and SHA12). The results are similar for both cases. The reason for this effect is that collecting the second component reduces the time t_2 and consequently the cycle time. This fact can be recognized also in Figure 5.

Figure 10 shows other plots of the production rate of the less concentrated component in a 3:1 (a) and a 1:3 (b) mixtures vs. the cycle number. In contrast to Figures 9b and 9d, the experimental conditions for Figure 10 are those which are optimal for the maximum production rate of the more concentrated component in a single-cycle regime. This time, the results show a remarkable increase in production rate in the second cycle. This effect can be explained mainly by the reduction of the competition of the more concentrated component. A maximized amount of this component is separated in the first cycle. In the third cycle, the production rate of less

concentrated component reaches its maximum. The differences among the results given by the four procedures of fraction collection are more pronounced in Figure 10 than in Figure 9. Again in these cases, the procedures doing fraction collection of the second component or both components (SHA2 and SHA12) allow for the highest production rates.

In Figure 11, the production rate of the second component of a 3:1 mixture is plotted vs. the cycle number for the SHA12 procedure, using the optimal parameters for the production of the first component (see Figure 10a). The corresponding recovery yields of the second component are also shown in this figure. In addition, the values of the maximum production rate attainable in the single-cycle case and the corresponding yield are shown on the axes. Obviously, recycling offers a considerable improvement in this case. Using a three-cycle regime, the production rate increases by 41%, while the re-
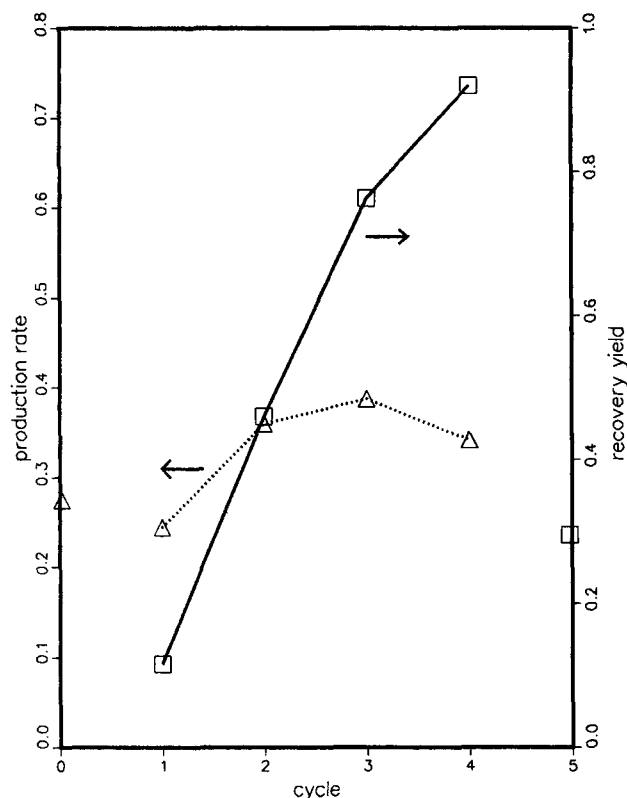
Figure 11. Production rate and recovery yield for component 2 in dependence on cycle number (SHA12-model), 3:1 mixture, optimal parameters for component 1.

The optimal values of the single cycle regime are shown on the axes.
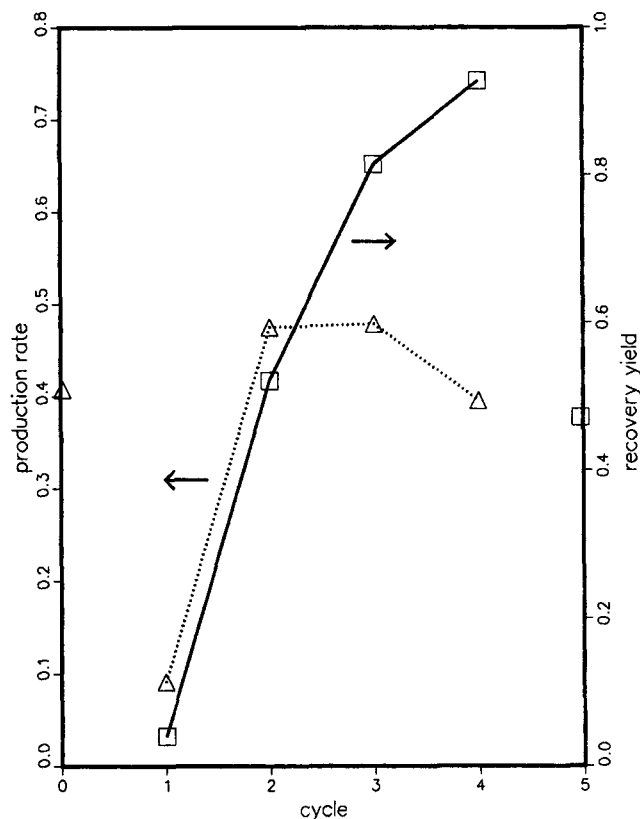

Figure 12. Production rate and recovery yield for component 1 in dependence on cycle number (SHA12-model), 1:3 mixture, optimal parameters for component 2.

The optimal values of the single cycle regime are shown on the axes.

covery yield is more than doubled. Such a recovery yield could be achieved in a single-cycle system only with a considerable loss in production rate (Table 2).

Figure 12 shows similar results for the production rate of the first component of a 1:3 mixture, using the optimal parameters for maximum production rate of the second component (see Figure 10b). The same conclusions can be drawn. We can achieve with this three-cycle regime a production rate 17% higher than that in the optimized single-cycle approach. The recovery yield increases from 48.7% to 81.4%.

To further demonstrate the application of recycling, we show in Figures 13 (solid lines) part of the chromatograms calculated for three consecutive injections in the three-cycle approach, with collection of purified fractions of both components during each cycle (SHA12), as discussed in Figure 11. Only the profiles of the fraction of interest are drawn, showing the collection of the second component. For comparison, consecutive chromatograms obtained in the optimized single-cycle regime are shown in dotted lines. Because the solid and dotted lines correspond to different values of the reduced velocity, mass fluxes are represented as a function of time, instead of concentrations. This representation shows again the superiority of the cyclic regime for these examples.

In this evaluation of recycling, one important aspect has not been considered. For easy comparison with the results obtained with the classical single-cycle mode, recycling was studied using the optimal values of the parameters calculated for the former

mode (k_1', ν, L_f). There are no reasons to assume that these parameters would also be optimum for recycling. The optimization of the experimental conditions in recycling mode was not the subject of the present work, however. Such an optimization is a considerable task which would have to include also the determination of the optimal cycle number. To demonstrate that the performance of recycling can further be improved and that the approach is highly flexible, Table 4 shows some results of parametric calculations using different, nonoptimal values of the reduced velocity. It also shows that at $\nu = 250$ the production rate of the three-cycle mode is still larger than that at $\nu = 171$, the optimal velocity for the single-cycle regime (Table 2). The price to be paid for increasing the production rate in this example is the drop in the recovery yield.

Finally one aspect mentioned in the characterization of the closed-loop approach of recycling should be quantified. In the periods of recycling this regime does not require fresh solvent. For the example discussed in Figure 13, the fraction of solvent saved compared with the requirement of the single-cycle mode is 24.9%, which is quite significant in view of the relative importance of solvent cost in the total cost of chromatographic purification.

Conclusions

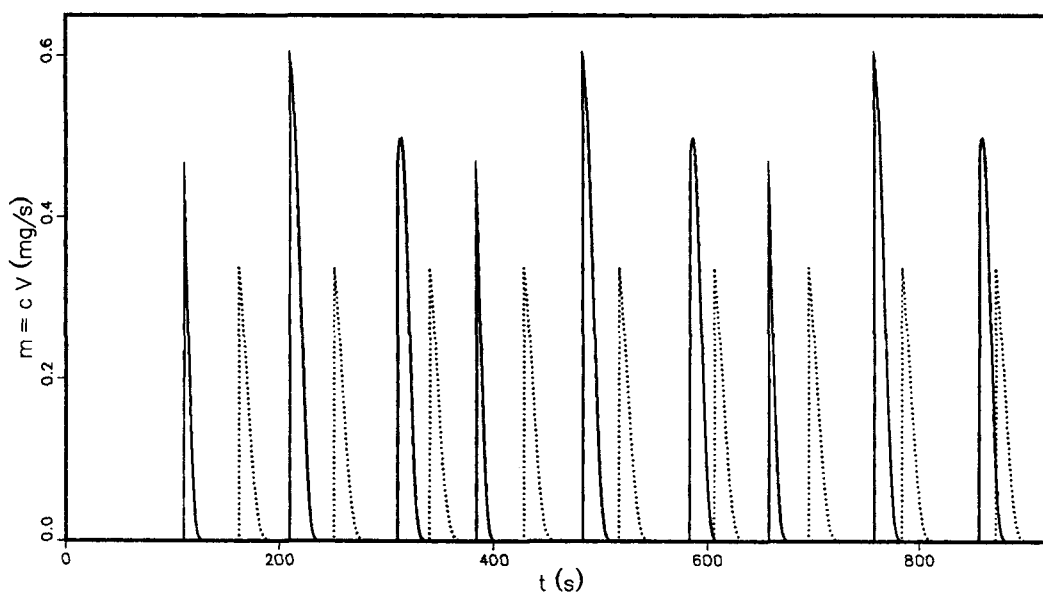Numerical calculations of different recycling procedures

Figure 13. Collected fractions of component 2 in a 3:1 mixture.

Solid lines: 3-cycle-regime with optimal parameters for production of component 1 in a single-cycle regime, 3 consecutive injections, SHA12-model; dotted lines: single-cycle regime, optimal parameters for the production of component 2, 9 consecutive injections.

demonstrate the great potential of this hitherto empirically applied principle. Due to the large number of parameters that have an influence on the success of the separation and to the intricacy of their effects, general conclusions are difficult to draw. If the required competitive equilibrium isotherms and mass-transfer data are available for the phase system and the feed used, the decision whether a recycling technique might favorably compete with a single-cycle regime can be drawn using our mathematical model.

On the basis of our present analysis of two examples of binary mixtures, the following tendencies can be considered as reasonable qualitative guidelines for such a decision. Recycling will always improve the recovery yield. In many cases, the production rate will decrease during recycling. In some attractive cases, however, recycling will increase both the recovery yield and the production rate. These situations are more probable for the production of a minor feed component. In such cases, instead of optimizing the cyclic regime which appears to be a formidable computational task, a more appropriate approach seems to be the optimization of the single-cycle mode with the objective function of maximum removal of the higher concentrated component in the first cycle.

The different procedures possible for the collection of frac-

tions during recycling do not lead to significantly different values of the recovery yield in the cases studied. However, it is advantageous to collect the more retained component during each cycle, as this reduces the cycle time and increases the production rate. The collection of the first eluted component has no essential additional effect, provided that there is no overlap between the bands of one cycle and those of the next one.

To use the full potential of the recycling method, however, the process as a whole has to be optimized.

Acknowledgment

Notation

a = parameter in isotherm Eq. 6
A_c = column area, $\pi/4\ d^2$, m^2
b = parameter in isotherm Eq. 6, L/g
C = liquid (mobile)-phase concentration, g/L
$C_E(t)$ = concentration at column inlet, g/L
C_{min} = concentration threshold to begin or end fraction collection, g/L
C_0 = concentration in the feed, g/L
d = column diameter, m
d_p = particle diameter, m
D_{ap} = apparent dispersion coefficient, m^2/s
D_m = molecular diffusion coefficient, m^2/s
F = phase ratio, $(1-\epsilon_T)/\epsilon_T$
F_i = integer connected with mode of collection of component i (0, no collection; 1, collection)
h = reduced plate height, Eq. 7
k' = retention factor

Table 4. Influence of Reduced Velocity on Recovery Yield and Production Rate for a 3-Cycle Regime with Fraction Collection (SHA12)*

ν	R_1 (mg/cm^2·s)	Y_1
171	0.478	0.814
200	0.509	0.754
250	0.543	0.662
300	0.523	0.545

* (1:3 mixture, $k_1' = 1.5$, $L_f = 0.0553$). $\nu = 171$ is the optimal value in the single-cycle regime (Table 2).

L = column length, m

L_f = loading factor, Eq. 9

M_{21} = change in composition during recycling [$M_{21} = (m_{2rec}/m_{2inj})/(m_{1rec}/m_{1inj})$]

m = mass, g

$m\cdot$ = mass flux, g/s

n = cycle number

N = number of components

N_p = number of theoretical plates

Pu = purity, $m_j/(m_1 + m_2)$

q = stationary phase concentration, g/L

q_s = saturation loading, g/L

R = production rate, Eq. 8, mg/cm^2·s

t = time, s

t_1 = time started collecting component 1, s

t_2 = tiem ended collecting component 2, s

t_{c1} = time ended collecting component 1, s

t_{c2} = time started collecting component 2, s

t_p = pulse width of the injection, s

t_R = retention time, s

t_0 = retention time of a nonretained component, s

u = linear velocity, $u = L/t_0$, m/s

v_{inj} = injected volume, L

$\dot{V}$ = volumetric flow rate, $\dot{V} = u A_c \epsilon_T$, L/s

V_c = volume of column, m^3

x = axial coordinate of column, m

Y = recovery yield, m_i/m_{iinj}

Greek letters

α = separation factor

ϵ_T = total porosity

ν = reduced velocity, Eq. 7

Subscripts

act = actual cycle

0 = initial values (at injection)

1 = first eluted component

2 = second eluted component

c = cut point

i = component rank of elution

inj = injected

k = running number for cycles

min = threshold value

n = running number of cycles

prev = previous cycle

rec = recycled

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