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The "VARICOL" Process: A New Multicolumn Continuous Chromatographic Process

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ABSTRACT

A new continuous chromatographic process is presented. This is in contrast to the known simulated moving bed (SMB) process which employs a synchronous shift of inlet/outlet lines. The basic principle of the new VARICOL process is based on a non-synchronous shift of the inlet/outlet valves in a multicolumn system. A numerical example compares the performances of the new VARICOL process to the well-known SMB process. This study shows that the VARICOL performances can be better than those of the SMB process. For example, a 5-columns VARICOL permits the same purities to be reached as a 6-columns SMB with the same productivity. Interest in the process is also validated experimentally. Both SMB and VARICOL are optimized to reach the highest achievable productivity for given outlet purities. The productivity of a 5-columns system can be improved 18.5% by using the VARICOL process.

I. INTRODUCTION

Different possible modes of production chromatography have been described, for example, by Wankat (1), Le Van et al. (2), and Nicoud and Bailly (3). These modes can be classified according to different criteria: for example, the process can be batch or continuous, systems can use a single column or can be multicolumn, eluent composition can be isocratic or gradient operated. Among these modes, continuous implementations using multicolumn

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schemes based on the simulated moving bed (SMB) concept are gaining a lot of interest. The purpose of this article is to present a new continuous multicolumn chromatographic implementation that shows advantages over SMB. This new process doesn't simulate a moving bed that constitutes a limiting case to this system.

II. PRESENTATION OF THE TMB AND SMB PROCESSES

The true moving bed (TMB) process, presented in Fig. 1, can be characterized by the common definition: "In a moving bed system for continuous countercurrent effect, solids move continuously in a closed loop past *fixed points* of introduction and withdrawal of feed and regenerant" (2).

The principle of the TMB process has been described in several articles [see, for instance, Charton and Nicoud (4), Storti et al. (5), Ruthven and Ching (6)], and its main features are summarized below.

- A countercurrent contact between liquid and solid phases is promoted in a column that can be divided in 4 different zones:

  Zone I: zone between the eluent and the extract lines
  Zone II: zone between the extract and the feed lines
  Zone III: zone between the feed and the raffinate lines
  Zone IV: zone between the raffinate and the eluent lines

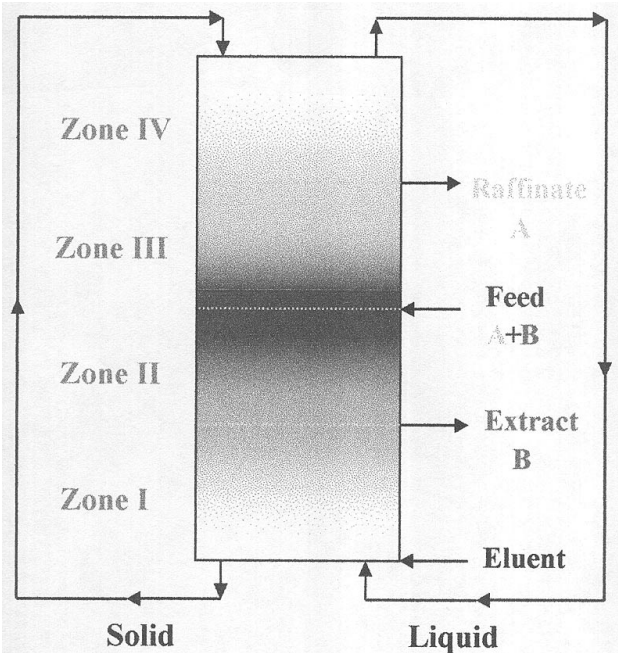

FIG. 1 Principle of the 4-zone true moving bed.

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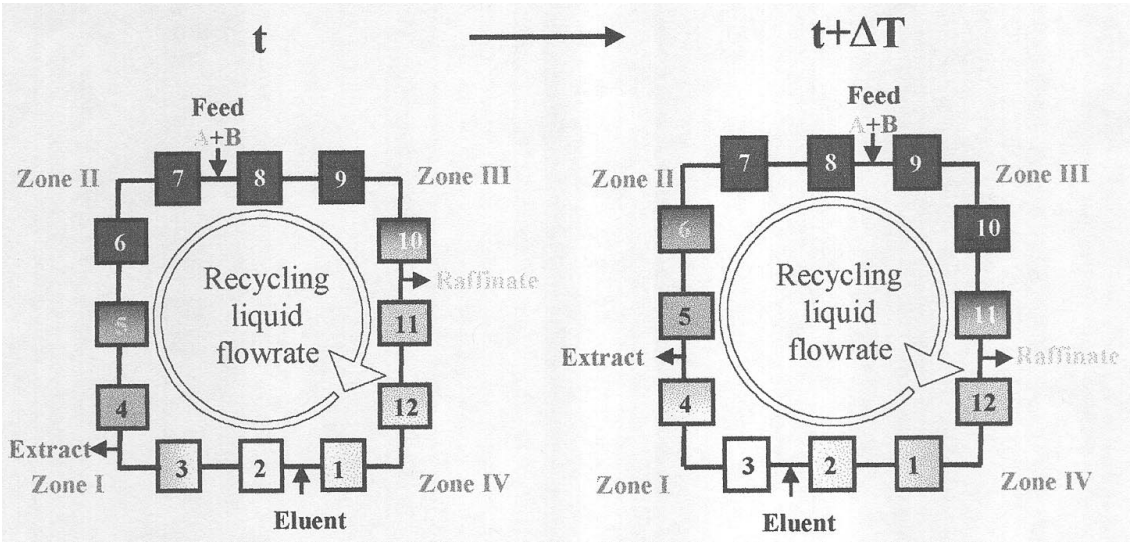

FIG. 2 Principle of an SMB (12 columns). All the inlet/outlet lines are shifted at every period ΔT.

- The solid flow rate is constant in all the system.
- The liquid flow rates vary according to the zone because of the inlet/outlet streams, with Q_{I}, Q_{II}, Q_{III}, and Q_{IV} being the respective flow rates in zones I, II, III, and IV.

In 1961 the UOP company patented a process allowing simulation of the motion of the solid via an adequate connection between columns as shown on Fig. 2 (7). This process, called simulated moving bed (SMB), thus appears as a simple way to implement the TMB practically. It is characterized by "periodically advancing downstream the point of introducing the feed stock and the desorbent while *simultaneously and equally advancing* downstream the point of withdrawal of raffinate and sorbate" (8), ". . . and the feed and desorbent inlet points and the product withdrawal points being translated along the column in *equal increments* by a stream distribution means" (9), ". . . in said process streams are periodically shifted *in unison* successively from one set of transfer points to the next in a downstream direction with respect to the flow of said pumparound . . ." (10).

Again, this process has been extensively described [see, for instance, Charton and Nicoud (4), Gattuso (11), Strube et al. (12)], and its key features are summarized below.

The positions of the inlet/outlet are switched at fixed intervals. It is convenient to refer the position of the lines as *Line(n)*, which means that at a given time a given inlet/outlet *Line* is connected at the inlet of column *n*. For instance, *Feed (3)* means that the feed line is connected at the inlet of column 3 while *Raff(8)* means that the raffinate line is connected at the inlet of column 8.

Using this definition, the system presented in Fig. 2 is referred to as *El(2)/Ext(4)/Feed(8)/Raff(11)* at time *t*. For this configuration the number of columns in zones I, II, III, and IV are, respectively, 2/4/3/3. The system status is thus completely defined by

	Inlet/outlet	No. of columns
at time t:	*El(2)/Ext(4)/Feed(8)/Raff(11)*	*2/4/3/3*

After a given time (the *period*) all the inlet/outlet positions are switched by one column and the system is described by

at time $t + \Delta T$:	*El(3)/Ext(5)/Feed(9)/Raff(12)*	*2/4/3/3*

After another period all the positions will again be switched by one column and the system will be described by

at time $t + 2 \times \Delta T$:	*El(4)/Ext(6)/Feed(10)/Raff(1)*	*2/4/3/3*

At time $t + 2 \times \Delta T$ the position of the raffinate will have been shifted from position 12 to position 1. *Position 1* can be written *position 13 modulo 12* ($[13]_{12}$).

This presentation can be generalized to any type of SMB containing N_c columns. For a SMB made of N_c columns, it is obvious that no position can exceed N_c. For the sake of simplicity, we will simply increment all the positions by one at every switch, and define all the positions *modulo* N_c (for instance $[8]_{N_c} = 3$ if $N_c = 5$).

If at a given time the SMB configuration is *El(e)/Ext(x)/Feed(f)/Raff(r)*, a simple investigation permits the number of columns contained in each zone to be determined

Zone I: $N_{c_1} = [x - e]_{N_c}$
Zone II: $N_{c_2} = [f - x]_{N_c}$
Zone III: $N_{c_3} = [r - f]_{N_c}$
Zone IV: $N_{c_4} = [e - r]_{N_c}$

Obviously, $N_{c_1} + N_{c_2} + N_{c_3} + N_{c_4} = N_c$.

The SMB operating mode is completely defined on Table 1.

TABLE 1
Global Representation of an SMB Configuration

	Inlet/outlet	No. of columns in each zone
at time t:	*El(e)/Ext(x)/Feed(f)/Raff(r)*	$N_{c_1}/N_{c_2}/N_{c_3}/N_{c_4}$
at time $t + \Delta T$:	*El*$([e+1]_{N_c})$*/Ext*$([x+1]_{N_c})$*/Feed*$([f+1]_{N_c})$*/Raff*$([r+1]_{N_c})$	$N_{c_1}/N_{c_2}/N_{c_3}/N_{c_4}$
at time $t + n*\Delta T$:	*El*$([e+n]_{N_c})$*/Ext*$([x+n]_{N_c})$*/Feed*$([f+n]_{N_c})$*/Raff*$([r+n]_{N_c})$	$N_{c_1}/N_{c_2}/N_{c_3}/N_{c_4}$

The main features of SMB systems (giving a practical implementation of the TMB presented in Fig. 1) are thus characterized by:

1. zones defined by the position of inlet/outlet lines
2. a fixed number of columns per zone.
3. zones of fixed length.
4. a synchronous shift of all the inlet outlet lines.

Features 2, 3, and 4 are consequences of the fact that SMB simulates the behavior of TMB.

The dissymmetry of the SMB resulting from the dead volume of the recycling pump in the closed loop disturbs the performances of the SMB process. This dissymmetry can, however, be corrected by adding a delay for the switch of the inlet/outlet line passing the recycling pump (13). In this case the shift of all the lines is not always synchronous to compensate for the technical imperfection of the real system and to get closer to the ideal symmetrical SMB system. (It is even noticeable that in one time per cycle all the inlet/outlet lines are shifted synchronously.) This asynchronous shift is, however, required for the dissymmetric system to be equivalent to the TMB.

III. PRESENTATION OF THE VARIZONE AND VARICOL PROCESSES

The basic idea of the Varizone process is to modify the TMB presented in Fig. 1 in order to allow a variation of the zone length over time (Fig. 3).

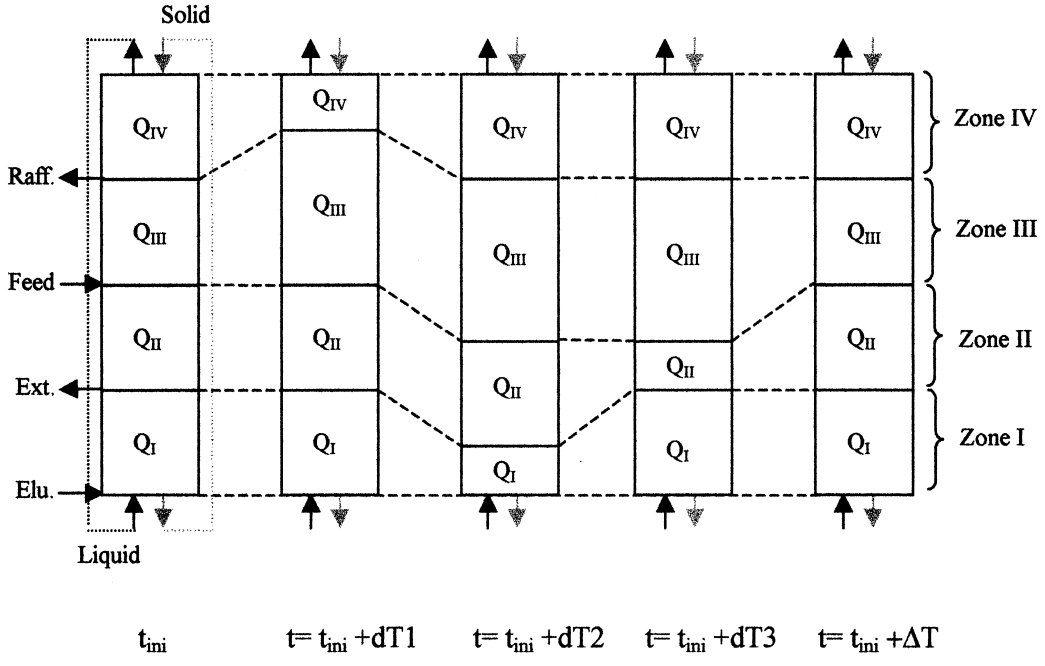

FIG. 3 The VARIZONE process.

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TABLE 2
Possible Representation of a VARICOL Process (first option)

	Inlet/outlet	No. of columns in each zone
at time t:	*El(e)/Ext(x)/Feed(f)/Raff(r)*	$N_{c_1}/N_{c_2}/N_{c_3}/N_{c_4}$
at time t + dT1:	*El([e + 1] $_{N_c}$)/Ext(x)/Feed(f)/Raff(r)*	$N_{c_1} - 1/N_{c_2}/N_{c_3}/N_{c_4} + 1$
at time t + dT2:	*El([e + 1] $_{N_c}$)/Ext(x)/Feed(f)/Raff([r + 1] $_{N_c}$)*	$N_{c_1} - 1/N_{c_2}/N_{c_3} + 1/N_{c_4}$
at time t + dT3:	*El([e + 1] $_{N_c}$)/Ext(x)/Feed([f + 1] $_{N_c}$)/Raff([r + 1] $_{N_c}$)*	$N_{c_1} - 1/N_{c_2} + 1/N_{c_3}/N_{c_4}$
at time t + ΔT:	*El([e + 1] $_{N_c}$)/Ext([x + 1] $_{N_c}$)/Feed([f + 1] $_{N_c}$)/Raff([r + 1] $_{N_c}$)*	$N_{c_1}/N_{c_2}/N_{c_3}/N_{c_4}$

In opposition to what occurs in the TMB process, the zone lengths of the VARIZONE are not fixed but are varied over time. Let us notice that, because of the zone length modulation, in opposition to TMB, *this system is not a steady-state process and the solid velocity is not constant with respect to the inlet/outlet lines.*

There are some oscillations of the zones length for which the process can be approximated in a system made of columns connected in series: the VARICOL process (14, 15). As described before, the zone lengths of the VARIZONE vary over time. These variations can, for instance, be periodic so that the system recovers its initial position after a given time as presented in Fig. 3. *In this article, we will focus the study on the periodic VARICOL process.*

Just as the SMB is a practical implementation of the classical TMB, the VARICOL is a practical implementation of the VARIZONE process.

Compared to the SMB operating mode defined in Table 1, the VARICOL process gives, *for instance*, the configuration described in Table 2. For this implementation the zone lengths are continuously oscillating by one column, the increase of one zone being compensated for by the decrease of the adjacent one.

For another implementation, the increase of one zone length can, for instance, be compensated by the decrease of the "opposite" zone, and the system is thus described in Table 3.

There are obviously other possible implementations, some of them will be presented in examples.

TABLE 3
Possible Representation of a VARICOL Process (other option)

	Inlet/outlet	No. of columns in each zone
at time t:	*El(e)/Ext(x)/Feed(f)/Raff(r)*	$N_{c_1}/N_{c_2}/N_{c_3}/N_{c_4}$
at time t + dT1:	*El(e)/Ext([x + 1] $_{N_c}$)/Feed(f)/Raff([r + 1] $_{N_c}$)*	$N_{c_1} + 1/N_{c_2} - 1/N_{c_3} + 1/N_{c_4} - 1$
at time t + ΔT:	*El([e + 1] $_{N_c}$)/Ext([x + 1] $_{N_c}$)/ Feed([f + 1] $_{N_c}$)/Raff([r + 1] $_{N_c}$)*	$N_{c_1}/N_{c_2}/N_{c_3}/N_{c_4}$

The key differences with respect to the SMB process appear immediately:

1. the zone lengths are not constant in time.
2. the number of columns per zone is not constant in time.
3. the inlet/outlet lines are not shifted simultaneously.
4. there is no equivalent constant solid flow rate: the solid flow rate of the equivalent VARIZONE process is not constant with respect to the inlet/outlet lines.

Though the oscillation introduces a strong perturbation in the system, it is surprisingly found that the performances of the VARICOL process can be better than the SMB performances.

The VARICOL process is a cyclic system. One cycle corresponds to the time required for each inlet/outlet lines to recover their initial position.

Within the overall cycle, the VARICOL may also exhibit subperiods. One period is, for example, the time required for all positions to be switched by one column. This study focuses on the periodic VARICOL processes. During this period the number of columns in each zone has been varied, and for pedagogical purposes it is useful to define an average number of columns per zone:

$\langle N_{c_1} \rangle$ = average number of columns contained in zone I during a period

$\langle N_{c_2} \rangle$ = average number of columns contained in zone II during a period

$\langle N_{c_3} \rangle$ = average number of columns contained in zone III during a period

$\langle N_{c_4} \rangle$ = average number of columns contained in zone IV during a period

The column repartition in a SMB system can be presented as

$$\text{SMB} \qquad N_{c_1}/N_{c_2}/N_{c_3}/N_{c_4}$$

We will represent the periodic VARICOL process as

$$\text{VARICOL} \qquad \langle N_{c_1} \rangle/\langle N_{c_2} \rangle/\langle N_{c_3} \rangle/\langle N_{c_4} \rangle$$

It must be noticed, however, that when the number of columns per zone has a real significance for SMB systems, the average numbers (usually nonintegers) defined for the VARICOL process have no real physical meaning and are simply used for convenience.

As an example, we will consider the periodic VARICOL process with 6 columns defined in Table 4. The evolution of the number of columns per zone is presented in Fig. 4. For this configuration, we can calculate the average number of columns in each zone during a complete period. In zone 1 the number of columns is equal to 1 during two quarters of the period and equal to 2 during the two other quarters. The average number of column in zone 1 is then

$$\langle N_{c1} \rangle = 2 \times \tfrac{1}{4} \times 1 + 2 \times \tfrac{1}{4} \times 2 = 1.5$$

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TABLE 4
VARICOL Configuration: Example with 6 Columns

	Inlet/outlet	No. of columns in each zone
at time t:	*El(e)/Ext(x)/Feed(f)/Raff(r)*	*1/2/2/1*
at time t + Δ*T/4*:	*El(e)/Ext([x + 1] $_{N_c}$)/Feed(f)/Raff(r)*	*2/1/2/1*
at time t + Δ*T/2*:	*El(e)/Ext([x + 1] $_{N_c}$)/Feed([f + 1] $_{N_c}$)/Raff(r)*	*2/2/1/1*
at time t + 3Δ*T/4*:	*El([e + 1] $_{N_c}$)/Ext([x + 1] $_{N_c}$)/Feed([f + 1] $_{N_c}$)/Raff(r)*	*1/2/1/2*
at time t + Δ*T*:	*El([e + 1] $_{N_c}$)/Ext([x + 1] $_{N_c}$)/Feed([f + 1] $_{N_c}$)/Raff([r + 1] $_{N_c}$)*	*1/2/2/1*

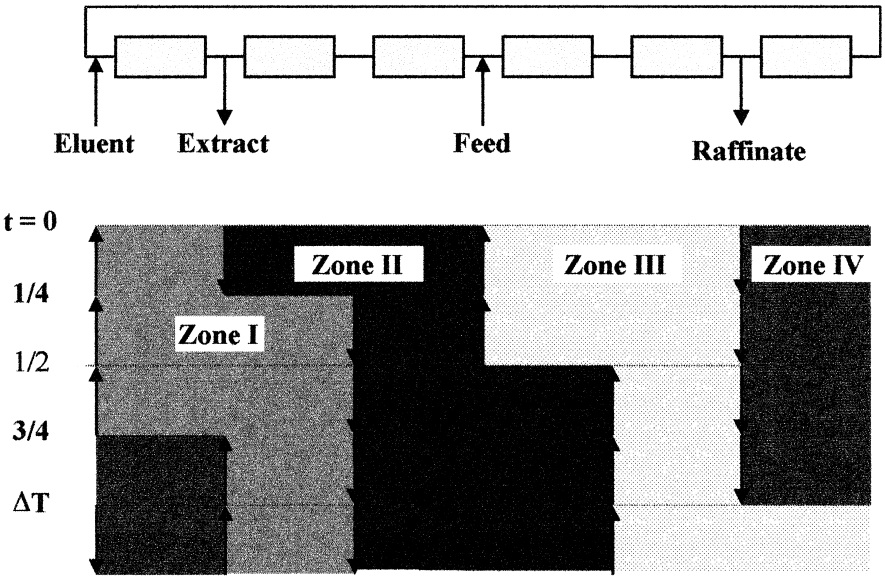

FIG. 4 Example of a 6-column VARICOL configuration: switching of the lines over a period.

TABLE 5
Calculation of the Average Number of Column in Each Zone of the VARICOL
(VARICOL configuration described on fig. 4)

		Number of column			
Fraction of the period	Duration	Zone 1	Zone 2	Zone 3	Zone 4
$0 \rightarrow \frac{1}{4}\Delta T$	$\frac{1}{4}\Delta T$	1	2	2	1
$\frac{1}{4}\Delta T \rightarrow \frac{1}{2}\Delta T$	$\frac{1}{4}\Delta T$	2	1	2	1
$\frac{1}{2}\Delta T \rightarrow \frac{3}{4}\Delta T$	$\frac{1}{4}\Delta T$	2	2	1	1
$\frac{3}{4}\Delta T \rightarrow \Delta T$	$\frac{1}{4}\Delta T$	1	2	1	2
Average number of column		$N_{c_1} = 1.5$	$N_{c_2} = 1.75$	$N_{c_3} = 1.5$	$N_{c_4} = 1.25$

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The same calculation can be performed in the three other zones as described in Table 5.

For this configuration, the average number of columns in each zone is then

$$\langle N_{c_1} \rangle = 1.5 \qquad \langle N_{c_2} \rangle = 1.75 \qquad \langle N_{c_3} \rangle = 1.5 \qquad \langle N_{c_4} \rangle = 1.25$$

IV. NUMERICAL SIMULATION OF THE VARICOL PROCESS

The simulation of a VARICOL process can obviously be performed with the classical tools used for modeling nonlinear chromatography processes. We have decided in this paper to use the mixing cells in series model as used in Ref. 4, of which the key features are presented below.

IV.1. Numerical Model

For each column of the process the mass balance for each compound i in the mixing cell k can be written:

$$C_i^{k-1} = C_i^k + \frac{t_0}{J}\frac{dC_i^k}{dt} + \frac{1-\varepsilon_e}{\varepsilon_e}\frac{t_0}{J}\frac{d\overline{C}_i^{\,k}}{dt} \tag{1}$$

where C_i^k is the concentration in the mobile phase
$\overline{C}_i^k$ is the equilibrium concentration in the stationary phase
J is the theoretical number of cells of the column
$t_0 = \dfrac{\varepsilon_e V_{col}}{Q_{col}}$ is the zero retention time of the column

The proper boundary conditions have to be used to properly simulate the process. Due to the periodic regime of the process, the boundary conditions are changing over time, according to the position of the different lines. The concentration $C_i^0[i_{col}]$ at the inlet of the column i_{col} can be easily calculated:

- If the feed line is connected at the inlet of the column $[i_{col}]$:

$$C_i^0[i_{col}] = \frac{(Q[i_{col}] - Q_{feed})C_i^J[i_{prev}] + Q_{feed}C_i^{feed}}{Q[i_{col}]} \tag{2}$$

- If the eluent line is connected at the inlet of the column $[i_{col}]$:

$$C_i^0[i_{col}] = \frac{(Q[i_{col}] - Q_{elu})C_i^J[i_{prev}]}{Q[i_{col}]} \tag{3}$$

- Else:

$$C_i^0[i_{col}] = C_i^J[i_{prev}] \tag{4}$$

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with:

$$\begin{cases} i_{\text{prev}} = i_{\text{col}} - 1 \text{ if } i_{\text{col}} > 1 \\ i_{\text{prev}} = N_{\text{col}} \text{ if } i_{\text{col}} = 1 \end{cases} \tag{5}$$

$$Q[i_{\text{col}}] = \text{flow rate in the column } i_{\text{col}}$$

The extract and raffinate concentrations can be simply calculated. If the outlet line is located after the column i_{col}, the outlet concentration for the compound i is equal to the concentration at the outlet of this column $C_i^J[i_{\text{col}}]$.

The column hydrodynamics will also be taken into account for this study.

The column efficiency is described by the classical "height equivalent to a theoretical plate" (HETP) value (16). In the case of preparative chromatography, the influence of the mobile phase velocity u can often be simplified into a linear relationship (17, 18):

$$H = L/J = a + bu \tag{6}$$

where L is the column length
J is the theoretical number of plates of the column

An experimental determination of this simplified Van Deemter's equation can be easily performed to estimate the parameters a and b. This relationship is required to estimate the number of plates of the experimental unit. When the internal flow rates are known, it is possible to calculate the column efficiency by knowing the column size. This can then be used to simulate numerically the process and to take into account the band broadening in the columns.

The pressure drop of the column is also a key parameter for the design of the chromatographic process. The influence of the mobile phase velocity on the pressure drop in a chromatographic column can be represented by following Darcy's law (19):

$$\Delta P/L = ku \tag{7}$$

This can be used to estimate the flow rates that can be used on the unit for a given column size (4).

IV.2. Numerical Comparison of the SMB and Varicol Processes

In order to give a comparison of the VARICOL with the SMB process, we will consider a simple numerical example.

The adsorption isotherms give the concentration in the stationary phase $\overline{C}$ versus the concentration in the mobile phase C when equilibrium is reached at

a given temperature. A competitive modified multicomponent Langmuir isotherm model (20) is used:

$$\overline{C}_{\mathrm{A}} = 0.5C_{\mathrm{A}} + \frac{1\ C_{\mathrm{A}}}{1 + 0.05C_{\mathrm{A}} + 0.075C_{\mathrm{B}}}$$
$$\overline{C}_{\mathrm{B}} = 0.5C_{\mathrm{B}} + \frac{1.5C_{\mathrm{B}}}{1 + 0.05C_{\mathrm{A}} + 0.075C_{\mathrm{B}}} \tag{8}$$

The feed composition is fixed to 10 g/L for each product. A continuous chromatographic process (SMB or VARICOL) will be designed to get a production of 1 metric ton a year. If we consider 8000 operating hours per year, the required feed flow rate is equal to 12.5 L/h.

Using the equilibrium theory (21, 22), one calculates a set of flow rates for the TMB allowing a complete separation neglecting any mass transfer limitation and hydrodynamic dispersion. The flow rates calculated according to this theory are given in Table 6. These flow rates permit obtaining a theoretical purity of 100% for both extract and raffinate on a TMB process with an ideal column (no mass transfer and no hydrodynamic resistance). These flow rates correspond to the optimal operating point of this process: the productivity is maximized and the eluent consumption is minimized.

In this numerical study the performance of the SMB and VARICOL process are compared by using the set of flow rates calculated for the ideal TMB process.

The feed flow rate can be related to the TMB solid flow rate:

$$Q_{\mathrm{feed}} = Q_{\mathrm{III}}^{\mathrm{TMB}} - Q_{\mathrm{II}}^{\mathrm{TMB}} = (1.44228 - 1.32684)\dot{M} \tag{9}$$

TABLE 6
TMB Flow Rates Calculated with the Equilibrium Theory in Order to Perform the Separation Corresponding to Relation (8)[a]

TMB conditions:
$Q_I^{TMB} = 2.0\dot{M}$
$Q_{II}^{TMB} = 1.32684\dot{M}$
$Q_{III}^{TMB} = 1.44228\dot{M}$
$Q_{IV}^{TMB} = 1.25975\dot{M}$

[a] $\dot{M}$ is the solid flow rate in the TMB.

For the given required feed flowrate, we can calculate the corresponding solid flow rate: $\dot{M} = 108.28$ L/h. The SMB internal flow rates and the shift period can be calculated by (23)

$$Q_i = Q_i^{\mathrm{TMB}} + \frac{\varepsilon}{1-\varepsilon}\dot{M}, \qquad i = \mathrm{I\ to\ IV} \tag{10}$$

$$\Delta T = \frac{1-\varepsilon}{\dot{M}} V_{\mathrm{col}} \tag{11}$$

The column volume is fixed to 3 L and the external porosity is equal to $\varepsilon_e = 0.4$.

The required operating conditions of the SMB process are given in Table 7.

Every column is expected to be equivalent to 50 plates, this number being assumed to be independent on the fluid velocity for the sake of simplicity. It has been checked that taking into account this dependence does not affect the conclusions. If the SMB flowrates given in Table 7 are used in a SMB, one obtains via numerical simulation the influence of the number of columns per zone on the extract and raffinate purities, as shown in Table 8.

The purities obtained at the outlet of the SMB seem to increase significantly when the number of column increases. Let us notice that this effect is due both to the increase of the global plate count of the system and to the increase of the number of subsections. For a fixed total number of columns, the repartition of these columns between the zones affects the individual as well as the average purity. For instance, if the total number

TABLE 7
SMB Flow Rates Calculated with the Equilibrium Theory in Order to Perform the Separation Corresponding to the Numerical Example[a]

SMB Conditions:	
Q_I	288.75 L/h
Q_{Feed}	12.5 L/h
Q_{Eluent}	80.16 L/h
$Q_{Extract}$	72.89 L/h
$Q_{Raffinate}$	19.76 L/h

[a] $\Delta T = 1.0$ minute.

TABLE 8
Purities Obtained via Simulation for Different SMB Configurations. The Average Purity Is Defined as the Average between Extract and Raffinate Purities

SMB configuration		Raffinate purity (%)	Extract purity (%)	Average purity (%)
Total number of column	Number of column per zone			
5	2/1/1/1	97.56	91.30	94.43
5	*1/2/1/1*	*98.55*	*93.13*	*95.84*
5	1/1/2/1	98.54	91.57	95.06
5	1/1/1/2	95.99	94.28	95.14
6	2/2/1/1	96.47	93.95	95.21
6	2/1/2/1	99.82	91.96	95.89
6	2/1/1/2	97.66	94.57	96.12
6	1/2/2/1	95.81	93.53	94.67
6	1/2/1/2	94.65	96.25	95.45
6	*1/1/2/2*	*98.49*	*95.15*	*96.82*
8	*2/2/2/2*	*98.38*	*97.95*	*98.17*

of columns is fixed to 5, the average purity is maximized for the 1/2/1/1 configuration.

The separation is now implemented in a VARICOL mode. Periodic VARICOL processes are simulated, using the same set of flow rates as for the SMB configurations. The switching period of the inlet/outlet lines is also $\Delta T = 1$ minute. In order to investigate by simulation the potential of the VARICOL concept, different column configurations are presented in Table 9 (the required valve switching are described in the Appendix for three of these configurations).

The performances of the VARICOL process can be compared with the SMB results presented in Table 8. In order to compare the two processes, we will compare the average purity obtained for a given total number of columns used for the separation.

Total Number of Columns = 5

Four SMB configurations are available with a total number of columns equal to 5. These four configurations have been simulated. The configuration having two columns in zone 2 (configuration 1/2/1/1) leads to a best average purity equal to 95.84%. As already stated, the mean number of column in each zone of the VARICOL can be a noninteger and we get therefore *an infinite number of VARICOL configurations*. With 5 columns (in total), five different configurations have been simulated and are presented in

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TABLE 9
Purities Obtained via Simulation for Different VARICOL Configurations. The Average Purity Is Defined as the Average between Extract and Raffinate Purities

VARICOL configuration		Raffinate purity (%)	Extract purity (%)	Average purity (%)
Total number of column	Average number of column per zone			
5	*1.25/1.25/1.25/1.25*	*97.89*	*95.98*	*96.94*
5	1.5/1/1/1.5	97.35	94.45	95.90
5	1/1.5/1.5/1	96.19	93.27	94.73
5	1/1/1.5/1.5	98.33	94.83	96.58
5	1.5/1.5/1/1	96.34	93.46	94.90
6	1.5/1.5/1.5/1.5	98.3	97.41	97.86
6	1.25/1.75/1.75/1.25	97.43	96.73	97.08
6	*1.75/1.25/1.25/1.75*	*98.67*	*97.12*	*97.89*
6	1.25/1.25/1.75/1.75	98.43	96.90	97.67
6	1.75/1.75/1.25/1.25	97.97	97.01	97.49
8	*2.5/1.5/1.5/2.5*	*98.95*	*97.81*	*98.38*
8	1.5/2.5/2.5/1.5	97.75	97.72	97.74
8	1.5/1.5/2.5/2.5	98.36	97.51	97.94
8	2.5/2.5/1.5/1.5	98.36	98.02	98.19

Table 9. The best result is obtained with the symmetrical configuration where the mean number of column in each zone is equal to 1.25. The simulated average purity is equal to 96.94%.

In conclusion, the 1.25/1.25/1.25/1.25 VARICOL configuration permits an increase in the average purity by 1.10% compared to the best SMB working with 5 columns. Over the five VARICOL configurations presented in Table 8, three configurations have a higher average purity compared to the best 5-columns SMB process. Other VARICOL configurations would probably allow further increases in the performances of the process. The complete optimization of the column distribution in the VARICOL process is beyond the scope of this article.

Total Number of Columns = 6

Six SMB configurations are available with a total number of columns equal to 6. The best average purity is obtained with the configuration having two columns in zones 3 and 4 (configuration 1/1/2/2). The average purity is then equal to 96.82%. This result can be compared with the performances of the best VARICOL operated with 5 columns described before. The average purity obtained with 5 columns on the VARICOL is slightly higher than the best per-

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formances obtained on the 6-columns SMB process: the purity is increased by 0.12%. This simulated result shows the potential of this new process: compared with a classical SMB unit operated with 6 columns, the VARICOL process allows the saving of 1 column for the same performances of the separation. This will lead to a lower cost of the chromatographic unit: only 5 columns are required, and the required amount of stationary phase is decreased by 16.7%. The operating pressure of the system can also be decreased by removing one column from the system. The VARICOL process consequently permits significant reduction in costs.

The best average purity obtained with the VARICOL process having a mean number of column equal to 6 was calculated for the 1.75/1.25/1.25/1.75 configuration (mean number of column equal to 1.75, 1.25, 1.25, and 1.75 in zones I, II, III, and IV, respectively). This configuration yields a mean purity of 97.89%. For a continuous chromatographic process with 6 columns, the VARICOL process is more efficient than any 6-column SMB. The VARICOL process allows the average purity to be increased by 1.07% compared to the best result obtained with the SMB.

Total Number of Columns = 8

The symmetrical SMB configuration has been simulated (2 columns in each zone). For this configuration the average purity is equal to 98.17%. Compared to the 6-column VARICOL process, the purity is only increased by 0.28% by adding two more columns to the system. Different VARICOL configurations with 8 columns have been simulated. The best performance is obtained with the 2.5/1.5/1.5/2.5 VARICOL configuration. This configuration allows a mean purity of 98.38% to be reached. The improvement of the performance is, however, smaller for a 8-column configuration, where the performances of the SMB are very close to the real countercurrent process (TMB).

This simulation study shows why there is great interest in comparing the VARICOL process to the SMB. Interest in the VARICOL process is particularly important where a continuous chromatographic systems having a low number of columns (5 or 6) is employed. Even if the oscillations introduce a perturbation of the system, the VARICOL performances are often better than the best results obtained with the SMB process.

V. EXPERIMENTAL

The performance improvement obtained with the VARICOL process with numerical examples is validated by experiment. A separation was performed with both SMB and the VARICOL process. The separation was optimized for both processes in order to compare their performances.

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V.1. Separation

The chiral separation of the 1,2,3,4-tetrahydro-1-naphthol racemate was studied. The following chromatographic conditions were used for the separation:

Sample: 1,2,3,4-tetrahydro-1-naphthol (Sigma-Aldrich)
Stationary phase: Chiralpak AD 20 μm (Chiral Technologies Europe, France)
Eluent: *n*-Heptane, HPLC grade (SDS, France)
2-Propanol, HPLC grade (SDS, France)
Trifluoroacetic acid, for synthesis (Sigma-Aldrich)
95/5/0.2 (v/v/v)
Temperature: 27°C

V.2. Experimental Apparatus

The separation is performed on the μ-lab, a pilot unit developed for the laboratory study of chromatographic separation. The picture of this unit is presented as Fig. 5. The μ-lab is a direct scale down of NOVASEP pilot and in-

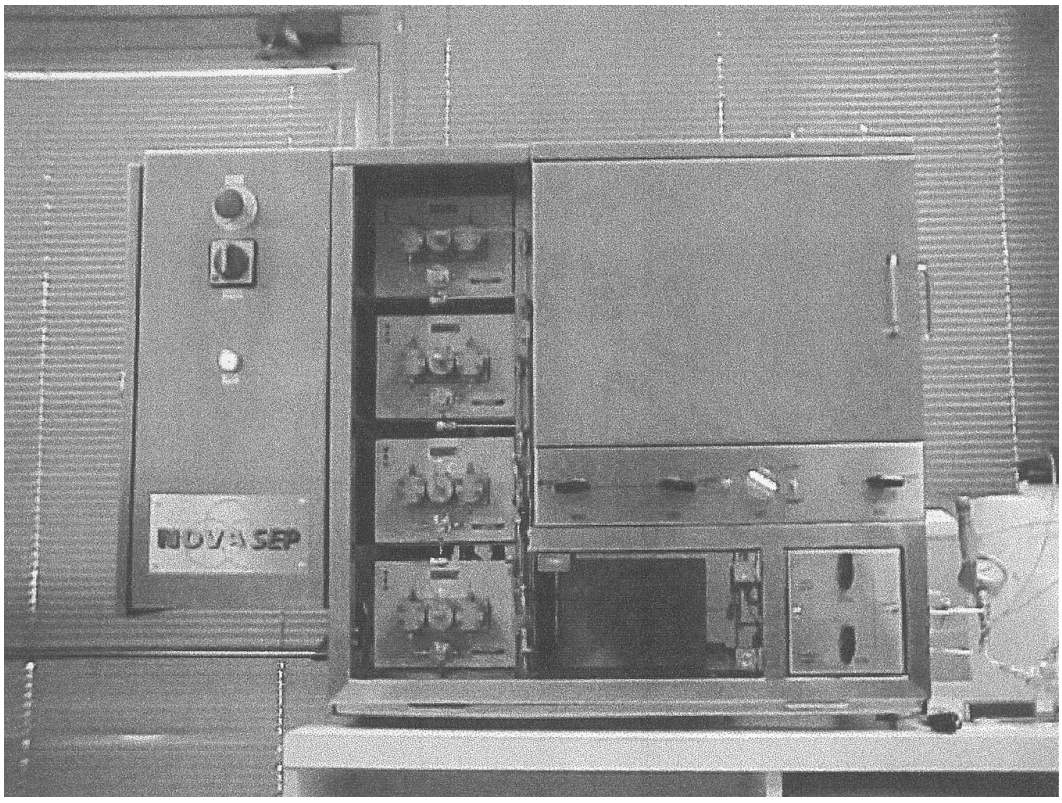

FIG. 5 Photograph of the pilot unit used for the experimental study.

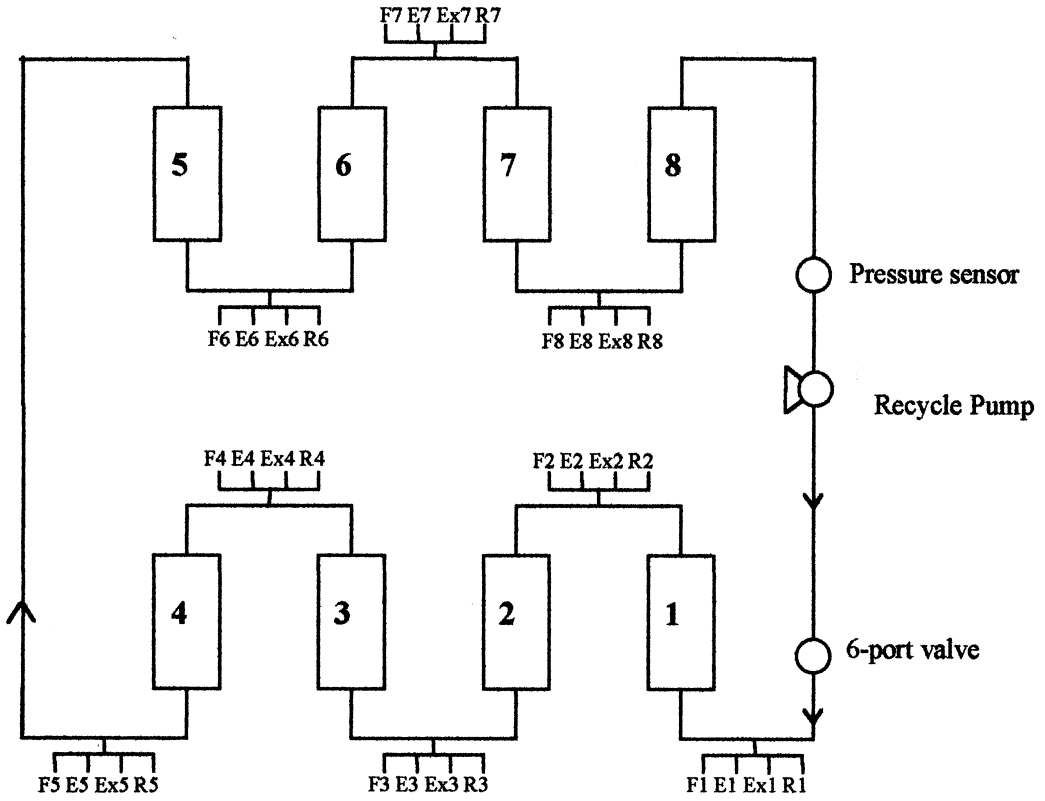

FIG. 6 Flow sheet of the μ-lab.

dustrial scale systems, and it permits small-scale separations to be performed of a few grams of product per day. The results obtained on the μ-lab can therefore, be directly transferred to pilot scale plants.

The flow sheet of the μ-lab unit is given in Fig. 6. The μ-lab is composed of a maximum number of eight columns (10 mm i.d., 100 mm length) connected in series. An HPLC pump (μ-pompe, ARMEN instrument, France) provides the appropriate recirculation flow rate through the recycling line. Four lines are connected to each column:

F*i*: Feed line connected to the feed pump
E*i*: Eluent line connected to the eluent pump
Ex*i*: Extract line connected to the extract pump
Raf*i*: Raffinate line connected to the raffinate pump

There are consequently eight lines of each type (eight columns system). At a given time, only one line of each type must be opened.

A 6-port valve is set on the recycling line at the inlet of the first column. This 6-port valve allows an internal sample to be collected and measures the internal concentration at the inlet of the first column. As the concentration pro-

files are circulated around the column loop, the collecting of the internal concentration at given collecting time allows the measurement of the internal concentration profile of the system. This profile is of major importance to optimize the process.

The μ-lab is controlled by a program implemented on a PC computer and analog input output cards. An oven is used to control and regulate the temperature of the columns and the valves on the unit.

The analysis is performed on a HP1090 system (Hewlett-Packard). Analytical conditions:

Eluent: *n*-Heptane / 2-propanol / trifuoroacetic acid 95/5/0.2 (v/v/v)
Stationary phase: Chiralcel OD 10μm
Flow rate: 1 mL/min
Temperature: 27°C
UV detector wavelength: 270 nm

V.3. Laboratory Study

The separation is first characterized on an analytical column (4.6 mm i.d., 250 mm length) packed with the stationary phase Chiralpak AD 20μm. This column is used to measure the adsorption isotherms of the two enantiomers and to characterize the column hydrodynamics. These data will be used to calculate the required operating flow rates for the two processes.

V.3.1. Adsorption Isotherms

The adsorption isotherms are measured by the retention time method (24) applied to a binary mixture. The slope of the isotherms at the origin is directly derived from the analytical injection of the racemate mixture. Five overloaded chromatograms are performed to fit the adsorption isotherms parameters.

The following modified competitive Langmuir adsorption isotherms are obtained:

$$\overline{C}_1 = 2.2C_1 + \frac{1.23C_1}{1 + 0.0647C_1 + 0.04655C_2}$$
$$\overline{C}_2 = 2.63C_2 + \frac{1.35C_2}{1 + 0.0647C_1 + 0.04655C_2} \qquad (12)$$

V.3.2. Column Hydrodynamics

The pressure drop is measured on the analytical column at different flow rates. The coefficient of Darcy's law is then fitted to these experimental data:

$$\Delta P/L = (632.3 \times 10^6)u \qquad \text{(SI units)} \qquad (13)$$

The column efficiency is also characterized on the analytical column. The influence of the fluid velocity on the HETP is measured. We obtain the following simplified Van Deemter's equations for the two enantiomers:

$$H_1 = 8 \times 10^{-5} + 0.200u \qquad \text{(SI units)} \tag{14}$$

$$H_2 = 8 \times 10^{-5} + 0.244u \qquad \text{(SI units)} \tag{15}$$

The mixing cells in series model is used to perform simulation of the process. This model therefore defines a fixed number of plates for the column. The difference of column efficiency between the two enantiomers can therefore not be considered in this numerical model. The influence of the flow-rate variation on the column efficiency in the different zones is also not taken into account in this model. However, the performances of the SMB are only slightly sensitive to the number of plates (25), and the system can be well simulated by calculating the HETP value obtained for the more retained compound and considering the mean internal flow rate in the process. This approximation is also valid for the VARICOL process, according to the tests performed by simulation.

V.3.3. Solubility of the Racemate Mixture

The solubility of 1,2,3,4-tetrahydro-1-naphthol in the eluent at 27°C, measured experimentally, is 25 g/L.

The influence of the feed concentration on the SMB productivity is described in Ref. 5. Productivity for the SMB is improved by increasing the feed concentration. This conclusion should be also valid intuitively for the VARICOL process. We chose to work with a feed concentration of 20g/L to avoid product precipitation in the system.

V.4. Comparison of the Two Processes with 5 Columns

The goal of the experimental tests was to compare the separation performances of the SMB and VARICOL processes. According to the first numerical results, the advantages of the new VARICOL process over the SMB seem to increase by decreasing the number of columns of the system. As a first experimental validation, we chose to compare the two processes with 5 columns.

Each zone of the process (SMB or VARICOL) corresponds to a concentration front (6):

- desorption front of the more retained compound in zone I
- desorption front of the less retained compound in zone II
- adsorption front of the more retained compound in zone III
- adsorption front of the less retained compound in zone IV

The goal of each zone is to retain the corresponding concentration front to avoid pollution of the extract or raffinate by the nondesired product.

We define the two following terms.

1. *Leakage in a zone*. The concentration front is not retained and a pollution of the neighboring zone occurs. Therefore:
   - leakage in zone I and/or zone III leads to a pollution of the raffinate outlet with the more retained compound and a loss of raffinate purity.
   - leakage in zone II and/or zone IV leads to a pollution of the extract outlet with the less retained compound and a loss of extract purity.
2. *Margin in a zone*. The concentration front is contained in the zone and is nullified before the zone outlet. The corresponding set of flow rates is then conservative.
   - margin in zone II and/or zone III: the feed flow rate could be increased without decreasing the purity of the outlets.
   - margin in zone I and/or zone IV: the eluent flow rate could be decreased without decreasing the purity of the outlets.

In order to compare the SMB and VARICOL processes, it is required to compare two optimized processes. The required extract and raffinate purities are fixed and the operating flow rates are optimized to reach the maximal productivity (highest feed flow rate). The optimization procedure is described in Ref. 26.

In zones I and IV, the flow rates are chosen to avoid leakage of:

- the more retained product in zone I
- the less retained product in zone IV

The margin in zones I and IV is, however, minimized to reach the minimal eluent consumption.

The target purity is fixed to about 95% for both extract and raffinate. The pollution of the extract and raffinate is only due to zones II and III. This constraint is used to simplify the optimization of the process: let us consider that 95% extract and raffinate purities are obtained with a given feed flow rate. For a given separation, if the pollution is only due to zones II and III, it is impossible to increase the feed flow rate without decreasing the extract and/or the raffinate purity without modification of the switching time.

V.4.1. Optimization of the SMB Process

In order to compare the different SMB configurations, we set the operating pressure of the SMB process. The internal pressure is related to the internal flow rates of the system. If the switching time is fixed for all these tests (ΔT = 0.83 minutes), the mean internal flow rate in the four SMB configurations

is almost similar and is closed to 23 mL/min, leading to a similar operating pressure. According to Eq. (13), the operating pressure is about 15 bar. For the simulation we consider there to be 80 plates for each column of the process according to Eq. (15).

Table 10 presents the optimal operating flow rates obtained by simulation to reach 95% purity for both extract and raffinate for the four feasible SMB configurations. The highest productivity is obtained with the 1-2-1-1 SMB column distribution (highest feed flow rate injected in the SMB).

The following optimal operating flow rates were calculated by simulation for the 1-2-1-1 configuration for an extract and raffinate purity of 95%:

$$Q_{\mathrm{I}} = 27.09 \text{ mL/min}$$

$$Q_{\mathrm{ext}} = 5.78 \text{ mL/min}$$

$$Q_{\mathrm{feed}} = 1.62 \text{ mL/min}$$

$$Q_{\mathrm{raf}} = 2.08 \text{ mL/min}$$

$$Q_{\mathrm{elu}} = 6.24 \text{ mL/min}$$

$$\text{Period} = 0.83 \text{ minute}$$

The separation was performed on the μ-lab unit. The internal concentration profile at half-period was measured and is compared to the simulated profile in Fig. 7.

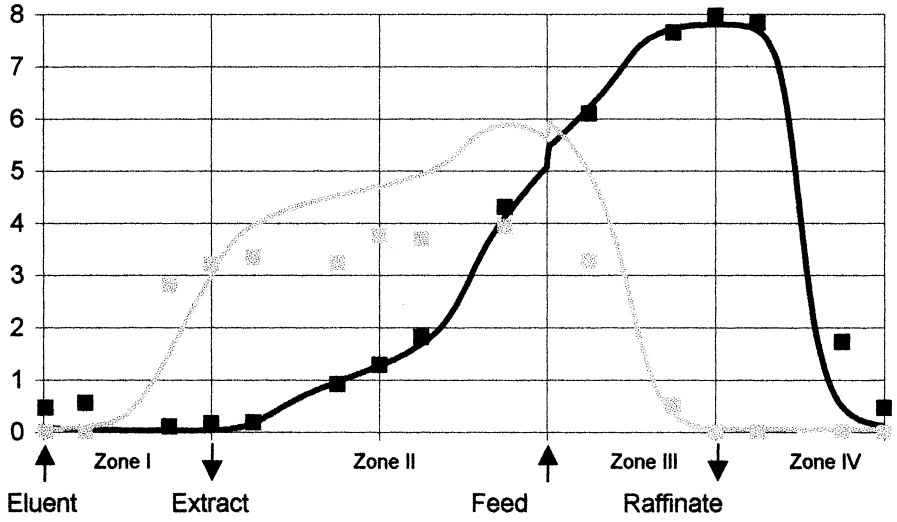

FIG. 7 SMB 1/2/1/1 internal concentration profile 1. Simulated profile:——. Experimental profile: ■.

The experimental purities* are

Extract: 93.0%
Raffinate: 92.5%

The experimental results are well fitted by the simulation. The retention is slightly lower than predicted (the experimental profile is shifted to the right) and a leak occurred from the less retained compound in zone IV.

The small difference between the predicted and experimental results could be easily compensated for by an adjustment of the flow to take into account the lower retention of the products. The recycling flow rate was reduced and the following set of flow rates were used:

$$Q_{\mathrm{I}} = 26.55 \text{ mL/min}$$

$$Q_{\mathrm{ext}} = 5.78 \text{ mL/min}$$

$$Q_{\mathrm{feed}} = 1.62 \text{ mL/min}$$

$$Q_{\mathrm{raf}} = 2.08 \text{ mL/min}$$

$$Q_{\mathrm{elu}} = 6.24 \text{ mL/min}$$

$$\text{Period} = 0.83 \text{ minute}$$

The experimental purities are then

Extract purity: 91.2%
Raffinate purity: 96.3%

The experimental internal concentration profile is plotted in Fig. 8. No leak can be observed in zones I and IV. According to the experimental internal concentration profile, the margins in zones I and IV are low. The eluent consumption could therefore not be reduced without leaking in these zones.

The small discrepancy between simulation and experiment is probably related to a small variation of the retention of the enantiomers between the tests in the laboratory (measurement of the adsorption isotherms) and the separation on the μ-lab unit. This difference could be simply explained by a small variation of the temperature. In fact, the optimal simulated flow rates are calculated to reach the absolute optimum of the process productivity: the safety margin in the different zones is minimized and the sensitivity of the system over a small variation of the retention is quite high. This could easily explain the small discrepancy observed between theory and experiment.

* For all the tests the measurement of the purities and of the eluent point of the profile is first performed after 30 cycles. The measurement is then repeated each 10 cycles until steady state is reached

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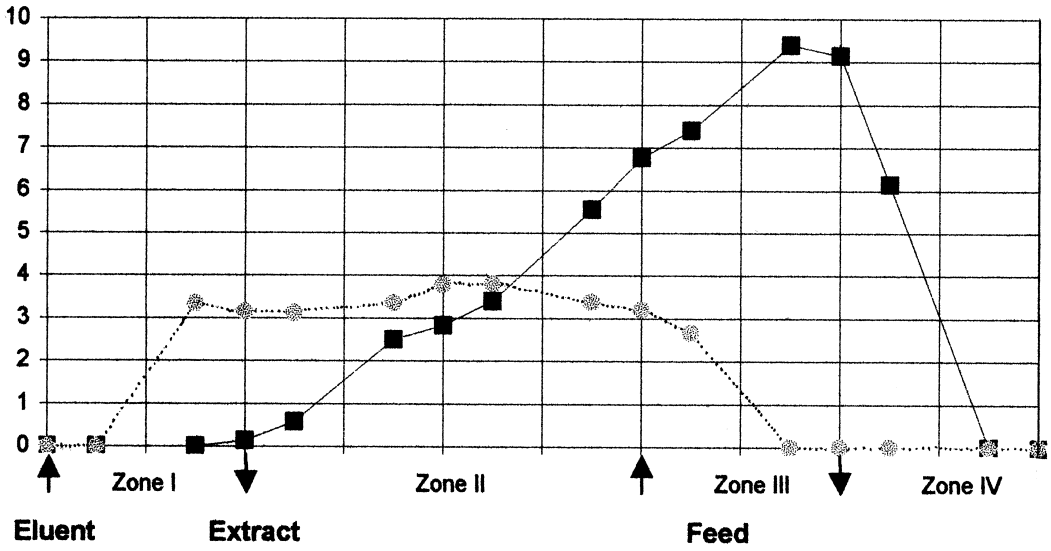

FIG. 8 SMB 1/2/1/1 experimental internal concentration profile 2.

The simulated purity of 95% was not achieved. However, our goal is to compare the two processes. The VARICOL process operating flow rates were therefore adjusted to get similar or higher purities for both extract and raffinate.

V.4.2. Optimization of the VARICOL Process

Two VARICOL configurations were studied experimentally.

V.4.2.1 First Configuration: VARICOL 1.25/1.25/1.25/1.25. A numerical optimization was performed to choose the required operating flow rates of the VARICOL process. The target purity was fixed to 95% for both extract and raffinate. The switching time was fixed to 0.83 minute (same period as the SMB process studied before).

The following optimal operating flow rates were obtained by simulation:

$$Q_{\mathrm{I}} = 26.60 \text{ mL/min}$$

$$Q_{\mathrm{ext}} = 5.07 \text{ mL/min}$$

$$Q_{\mathrm{feed}} = 1.65 \text{ mL/min}$$

$$Q_{\mathrm{raf}} = 2.15 \text{ mL/min}$$

$$Q_{\mathrm{elu}} = 5.57 \text{ mL/min}$$

$$\text{Period} = 0.83 \text{ minute}$$

The separation was performed on the μ-lab unit.

The experimental purities are:

Extract: 92.6%
Raffinate: 96.2%

Analysis of the eluent point* showed that the less retained compound was leaking from zone IV. A small shift of the profile to the right was therefore assumed (the products were less retained than predicted by simulation, as already observed for the SMB configuration).

The operating flow rates were slightly modified to avoid the leak between zones IV and I. As for the SMB process, the recycling flow rate was decreased to compensate for the lower retention of the products.

The following set of flow rate was tested experimentally:

$$Q_{\mathrm{I}} = 26.00 \text{ mL/min}$$

$$Q_{\mathrm{ext}} = 5.07 \text{ mL/min}$$

$$Q_{\mathrm{feed}} = 1.65 \text{ mL/min}$$

$$Q_{\mathrm{raf}} = 2.15 \text{ mL/min}$$

$$Q_{\mathrm{elu}} = 5.57 \text{ mL/min}$$

$$\text{Period} = 0.83 \text{ minute}$$

The experimental purities are

Extract: 92.7%
Raffinate: 96.9%

Both extract and raffinate purities were higher than those obtained with the SMB process. The extract purity increased from 91.2 to 92.7% and the raffinate purity from 96.3 to 96.9%. No leaks in zones I and IV were measured on the eluent point.

This VARICOL configuration permits higher purities to be reached for both the extract and raffinate compared with the 5-column SMB process. These

* The internal concentration profile cannot be measured by the classical way used to measure the SMB internal concentration profile (the profile doesn't reach a steady state and fluctuates during the cycle). However, it is possible to characterize the leakage between zones I and IV (respectively pollution from the more retained compound in the raffinate and from the less retained compound in the extract) by an appropriate collect of an internal concentration in the recycling loop. The leakages between zones I and IV can be characterized by the concentration at the eluent point between two switches of the corresponding line. In SMB this point is collected in the middle of the period at the position of the eluent line. For the VARICOL process the eluent line is also switched periodically and the collection can be performed half a period after the switch of the eluent line on the collecting point. On our experimental unit the collecting valve is set at the inlet of column 1; when the eluent line switches to position 1, the collection is performed after half a period.

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higher purities were obtained with an increase of the feed flow rate equal to 1.8%, leading to an improvement of the productivity of the system of 1.8%.

The main improvement obtained with this VARICOL configuration is that the eluent flow rate was decreased by 10.7% (5.57 instead of 6.24 mL/min for the SMB process). Even if the margin in zones I and IV cannot be evaluated for the VARICOL process (the internal concentration profile was not measured), the results of the simulation seem to be validated, i.e., eluent consumption can be reduced by using the VARICOL process with the 1.25/1.25/1.25/1.25 column configuration.

For separation on an industrial scale, the cost of the eluent recovery (loss, energy required for the evaporation, etc.) represents an important part of the separation cost and has to be optimized. The VARICOL 1.25/1.25/1.25/1.25 is therefore very attractive compared with the SMB 5-column configuration.

V.4.2.2 Second Configuration: VARICOL 1/1.5/1.5/1. According to Table 10, the SMB productivity is improved for the 1/2/1/1 and 1/1/2/1 configurations. Injecting the feed solution between zones II and III and increasing the number of column in these two zones is favorable for improving the productivity of the process. On the other hand, increasing the number of columns in zone I or zone IV leads to smaller productivity (smaller feed flow rate), but eluent consumption can be significantly reduced.

Another VARICOL configuration has been tested experimentally. In order to improve the productivity of the system, the number of columns in zones II and III was increased by using 1.5 columns in each zone. One column was then used in both zones I and IV, as for the SMB 1/2/1/1 configuration.

A numerical optimization was performed to choose the required operating flow rates of the VARICOL process. The target purity was fixed to 95% for both extract and raffinate. The switching time was fixed to 0.83 minute (same period as the SMB process studied before).

TABLE 10
SMB Optimal Operating Flow Rates for an Extract and Raffinate Purity of 95% (simulated results)

Configuration	Q_{feed} (mL/min)	Q_{eluent} (mL/min)	Q_I (mL/min)
2-1-1-1	0.94	5.294	26.48
1-2-1-1	1.62	6.24	27.09
1-1-2-1	1.31	5.87	27.1
1-1-1-2	0.82	5.81	27.69

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The following optimal operating flow rates were obtained by simulation:

$$Q_I = 27.04 \text{ mL/min}$$

$$Q_{ext} = 5.77 \text{ mL/min}$$

$$Q_{feed} = 1.82 \text{ mL/min}$$

$$Q_{raf} = 2.27 \text{ mL/min}$$

$$Q_{elu} = 6.22 \text{ mL/min}$$

$$\text{Period} = 0.83 \text{ minute}$$

The separation was performed experimentally on the μ-lab unit. As already observed for the first experimental study, a leak was observed in zone IV for the less retained product. The lower retention of the products can be compensated for by an adjustment of the recycling flow rate.

The following set of flow rates was then

$$Q_I = 26.5 \text{ mL/min}$$

$$Q_{ext} = 5.77 \text{ mL/min}$$

$$Q_{feed} = 1.82 \text{ mL/min}$$

$$Q_{raf} = 2.27 \text{ mL/min}$$

$$Q_{elu} = 6.22 \text{ mL/min}$$

$$\text{Period} = 0.83 \text{ minutes}$$

The experimental purities are:

Extract: 94.8%
Raffinate: 98.0%

No leaks in zones I and IV could be observed at the eluent point. The experimental purities were both much higher than those obtained in the SMB mode (extract, 91.2%; raffinate 96.3%).

The operating flow rates were therefore slightly modified to optimize the injected feed flow rates:

$$Q_I = 26.8 \text{ mL/min}$$

$$Q_{ext} = 5.82 \text{ mL/min}$$

$$Q_{feed} = 1.92 \text{ mL/min}$$

$$Q_{raf} = 2.32 \text{ mL/min}$$

$$Q_{elu} = 6.22 \text{ mL/min}$$

$$\text{Period} = 0.83 \text{ minute}$$

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The experimental purities are:

Extract: 92.4%
Raffinate: 97.7%

No leaks in zones I and IV could be observed at the eluent point. Both the extract and raffinate purities are higher than those obtained on the SMB 1/2/1/1 configuration by using this set of flow rates.

The VARICOL 1/1.5/1.5/1 configuration allows for a major improvement of the productivity compared to the SMB process: the injected feed flow rate was increased by 18.5%. No significant improvement was obtained with this VARICOL configuration regarding eluent consumption.

VI. TENTATIVE COMPARISON BETWEEN THE VARICOL AND THE SMB PROCESSES

Our first numerical and experimental results show that the ability of the VARICOL process to handle the separation of a binary mixture is very attractive, and that the performances are often better than those obtained with SMB. The main results obtained on these two examples (as well as on the examples presented in Ref. 13) are presented below.

Key Differences (user viewpoint)

From the user point of view, the most amazing feature of the VARICOL process consists in its ability to process and to deliver continuous streams without reaching steady state. The VARICOL process is asymptotically equivalent to the VARIZONE process which doesn't reach a steady state regime like the true moving bed process. This feature makes it especially difficult to determine (and even to define) the internal profiles.

The column distribution in the VARICOL process is a free parameter that can be optimized according to the separation. For the first time this new degree of freedom permits adjustment of the separation system depending on the objective function: optimization of eluent consumption or optimization of the productivity.

For a Given Configuration (columns and flow rates) Higher Purities Are Obtained with the VARICOL

Different SMB and VARICOL configurations were studied numerically in Part IV. Higher purities were obtained with VARICOL compared with SMB when the same set of flow rates as calculated by equilibrium theory were used.

For example, when the 6-columns configuration was studied:

- The best results for the SMB were obtained with the 1/1/2/2 configuration, leading to and extract and raffinate purity equal to 95.15 and 98.49%, respectively.

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- The best performance of the 6-columns VARICOL process was obtained with the column configuration 1.75/1.25/1.25/1.75. Both the extract and raffinate purities were increased compared to the results of the SMB:

  Extract purity of 97.12% for the VARICOL process; 95.15% for the SMB

  Raffinate purity of 98.67% for the VARICOL process; 98.49% for the SMB

All possible 6-columns configurations of the SMB were studied in this simulated example. On the other hand, the number of VARICOL configurations is infinite and only a few cases were presented. The performances of the 6-columns VARICOL could therefore be further improved by an optimization of the column distribution in the different zones.

VARICOL Can Save Columns

According to the numerical study, the simulated VARICOL process can even lead to savings in one column of the unit (5-column VARICOL compared with the 6-column SMB). The improvement of the VARICOL process seems to be more important for a small number of columns.

Saving one column has a great influence on process economics:

- The required amount of stationary phase can be reduced. This can have a major influence on the separation cost, mainly for chiral applications, where the chiral stationary phase is often expensive and can represent an important part of the separation cost.
- The operating pressure drop of the system is reduced, reducing the cost of the required chromatographic columns.
- Saving one column permits the operating flow rates to be boosted without increasing the pressure drop of the system. This allows a great increase of productivity.

TABLE 11
Comparison of the Optimized SMB and

	Q_I (mL/min)	Q_{II} (mL/min)	Q_{III} (mL/min)	Q_{IV} (mL/min)
SMB 1/2/1/1	26.55	20.77	22.39	20.31
VARICOL 1.25/1.25/1.25/1.25	26.00	20.93	22.58	20.43
VARICOL 1/1.5/1.5/1	26.8	20.98	22.9	20.58

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For a Given Target Purity, Productivity Is Higher for the VARICOL

According to the experimental example presented in Part V, the productivity of the VARICOL can be improved compared to the SMB for the same target purity. In this experiment the flow rates are optimized to reach similar purities for both SMB and VARICOL processes with maximal productivity. With a 5-columns VARICOL (1/1.5/1.5/1 configuration) it is possible to increase the productivity by 18.5% compared to the optimized 5-columns SMB process (1/2/1/1) without increasing the eluent consumption.

For a Given Target Purity, Eluent Consumption Is Lower for the VARICOL

According to the experimental example presented in Part V, the eluent consumption of the VARICOL can be reduced compared to the SMB for the same target purity. In this experiment the flow rates are optimized to reach similar purities for both SMB and VARICOL processes with maximal productivity. With a 5-columns VARICOL (1.25/1.25/1.25/1.25 configuration) it is possible to reduce the eluent consumption by 10.7% compared to the optimized 5-columns SMB process (1/2/1/1) with similar productivity for both processes.

Optimum Flow Rates are Different for VARICOL and SMB

Table 11 compares the optimized experimental flow rates for the SMB 1/2/1/1 and the two VARICOL processes tested for this study.

There is an important gap between the SMB and the VARICOL flow rates in the different zones operated with the same switching period. The experimental flow rates are optimized for the separation in order to reach maximal

VARICOL Flow Rates (experimental results)

Q_{Elu} (mL/min)	Q_{Ext} (mL/min)	Q_{Feed} (mL/min)	Q_{Raf} (mL/min)	Period (min)
6.24	5.78	1.62	2.08	0.83
5.57	5.07	1.65	2.15	0.83
6.22	5.82	1.92	2.32	0.83

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productivity. According to the experimental study, the optimal flow rates are different:

- Between the SMB and the VARICOL
- Between two configurations of the SMB
- Between two configurations of the VARICOL

The required flow rates in the different zones are linked to the number of column of the zones. Increasing the number of column in a zone increases both the number of plates and the number of subsections of the zone. The retention of the concentration front in the zone can then be improved. This is valid for both the SMB and the VARICOL:

- If the number of columns is decreased in zone I or II, the corresponding flow rates have to be increased to avoid the leakage of, respectively, the more retained product in zone I and the less retained product in zone II.
- If the number of columns is decreased in zone III or IV, the corresponding flow rates have to be decreased to avoid the leakage of, respectively, the more retained compound in zone III and the less retained compound in zone IV.

This evolution of the required internal flow rates is observed in the experimental optimized flow rates presented in Table 11. As an example, if the SMB 1/2/1/1 is compared with the VARICOL 1.25/1.25/1.25/1.25, we can see that:

- Zone I. More columns for the VARICOL: the flow rate is reduced without any leakage of the more retained enantiomer.
- Zone II. Less columns for the VARICOL: the flow rate is increased to avoid the leakage of the less retained enantiomer.
- Zone III. More columns for the VARICOL: the flow rate is increased without any leakage of the more retained compound.
- Zone IV. More columns for the VARICOL: the flow rate is increased without any leakage of the less retained compound.

According to these results, the model is very reliable in predicting the experimental behavior of the system. The eluent flow rate is equal to $Q_{elu} = Q_I - Q_{IV}$. As Q_I is reduced and Q_{IV} is increased, the required optimal eluent flow rate is logically smaller than for the SMB process.

An economic study is required to select the best VARICOL configuration, depending on the separation problem:

- Optimization of the productivity
- Optimization of the eluent consumption
- Optimization of the purities

The VARICOL process can be perfectly adapted to the separation problem by changing the column distribution in the different zones.

According to this study, the value of the VARICOL over the SMB seems to be maximal for systems with a low number of columns.

VII. CONCLUSION

The well-known SMB process and the new VARICOL process each permit continuous separation of a binary mixture in two pure streams via an appropriate shift of injection-collection lines between columns. However, whereas the SMB is made of well-defined zones containing a fixed number of columns, the VARICOL is made of zones of variable length containing a variable number of columns (and thus the average number of columns contained in a zone is noninteger). VARICOL therefore avoids the constraints of constant zone length and constant solid flow rate (equivalent to a moving bed).

By using both theoretical and experimental results, we have shown that for some special variations of zone length and equivalent solid flow rate, productivity and eluent consumption are more favorable for the VARICOL process than for the SMB process. For instance, the performance of a 6-columns SMB can be obtained with a 5-columns VARICOL.

We are aware that this work is not complete and that several important questions are still to be answered:

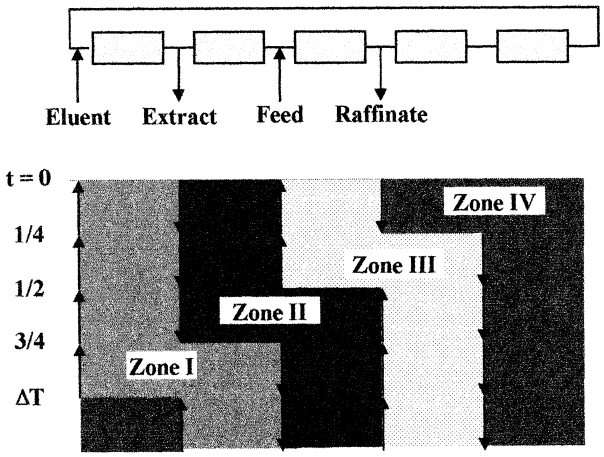
- Is it always possible to improve SMB performance by using the VARICOL concept?
- How can we define a strategy for the global optimization of a VARICOL process (optimal choice of column distribution)?
- Can we define some rules of thumb for predicting when the VARICOL process should be chosen over SMB?
- Are there other connections that allow maximal use made of columns?

By offering a new degree of freedom and breaking some constraints, we are convinced that the VARICOL concept will open doors to more sophisticated and efficient chromatographic processes. The VARICOL process opens a new branch of chromatographic modes beside the existing elution, recycling, and continuous modes like SMB.

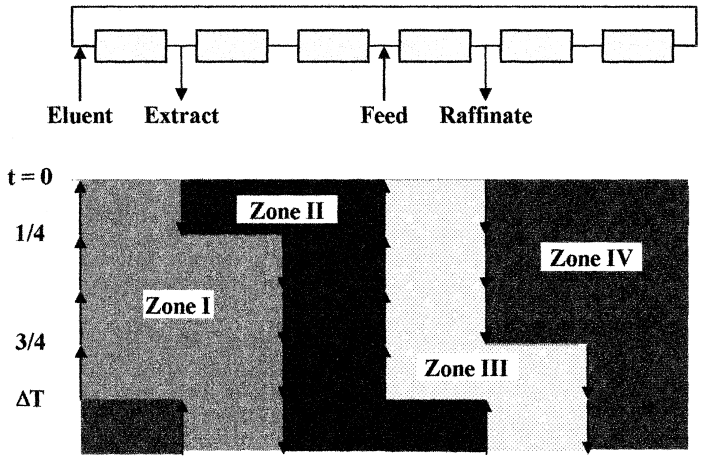
APPENDIX: SWITCHING OF THE VALVES FOR THREE VARICOL CONFIGURATIONS

This appendix describes the required valve switching of three VARICOL configurations. We choose to illustrate the VARICOL configurations presented in the report, leading to the best performances in Table 8.

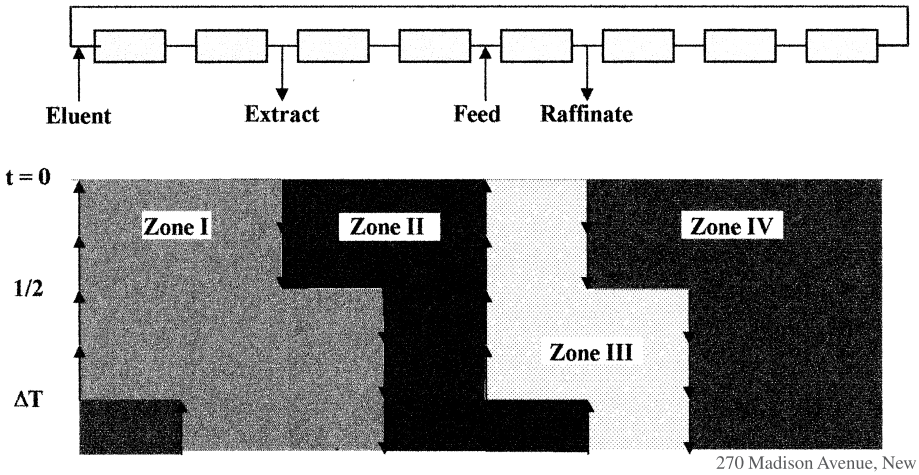
5-Columns VARICOL: 1.25/1.25/1.25/1.25 Configuration



6-Columns VARICOL: 1.75/1.25/1.25/1.75 Configuration



8-Columns VARICOL: 2.5/1.5/1.5/2.5 Configuration



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NOTATION

a, b	coefficients relating the height equivalent to a theoretical plate to the mobile phase velocity
C_i	concentration in the liquid phase, compound i
$\overline{C}_i$	concentration in the solid phase, compound i
C_i^{feed}	feed concentration, compound i
H	height equivalent to a theoretical plate
J	number of mixing cells of the column
k	parameter relating the pressure drop to the mobile phase velocity
L	column length
$\dot{M}$	solid flow rate
N_{c}	total number of columns
$N_{\text{c}i}$	number of columns in zone i
$\langle N_{\text{c}i} \rangle$	average number of columns contained in zone i during 1 period (VARICOL)
$Q[i_{\text{col}}]$	flow rate in the column i_{col}
Q_i	internal flow rates in zone i
Q_i^{TMB}	TMB internal flow rates in zone i
Q_{feed}	feed flow rate
u	superficial mobile phase velocity
V_{col}	column volume
ΔP	pressure drop
ΔT	period
ε_{e}	external porosity

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REFERENCES

1. P. C. Wankat, *Large Scale Adsorption and Chromatography*, CRC Press, Boca Raton, FL, 1986.
2. M. D. Le Van, G. Carta, and C. Yon, "Adsorption and Ion Exchange," in *Perry's Handbook of Chemical Engineering*, 7th ed., Section 16, McGraw-Hill, New York, NY, 1997.
3. R. M. Nicoud and M. Bailly, "Choice and Optimization of Operating Mode in Industrial Chromatography," in *Proceedings of the 9th International Symposium on Preparative and Industrial Chromatography, PREP 92, Nancy*, April 1992, pp. 205–220.
4. F. Charton and R. M. Nicoud, "Complete Design of a Simulated Moving Bed," *J. Chromatogr. A, 702*, 97–112 (1995).
5. G. Storti, M. Masi, S. Carra, and M. Morbidelli, "Modelling and Design of Simulated Bed Adsorption Units," *Prep. Chromatogr.*, 1(1), 1–27 (1988).

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6. D. M. Ruthven and C. B. Ching, "Counter-Current and Simulated Counter Current Adsorption Separation Processes," *Chem. Eng. Sci., 44*, 1011–1038 (1989).
7. D. B. Broughton, US Patent 2,985,589 (1961).
8. D. B. Broughton, US Patent 3,291,726 (1966).
9. D. M. Boyd, US Patent 3,268,605 (1966).
10. D. M. Boyd, US Patent 3,266,604 (1966).
11. M. J. Gattuso, "UOP Sorbex® Simulated Moving Bed (SMB) Technology. A Cost Effective Route to Optically Pure Products," *Chim. Oggi*, (September 1995).
12. J. Strube, U. Altenhöner, M. Meurer, H. Schmidt-Traub, and M. Schulte, "Dynamic Simulation of Simulated Moving Bed Chromatographic Processes for The Optimization of Chiral Separations," *J. Chromatogr. A, 769*, 81–92 (1997).
13. G. Hotier and R. M. Nicoud, US Patent 5,578,215 (1996).
14. M. Bailly, P. Adam, O. Ludemann-Hombourger, and R. M. Nicoud, US Patent Application 09/208,765.
15. M. Bailly, P. Adam, O. Ludemann-Hombourger, and R. M. Nicoud, French Patent Application 98/13.600 (1998).
16. J. J. Van Deemter, F. J. Zuiderweg, and A. Klinkenberg, *Chem. Eng. Sci., 5*, 271–289 (1956).
17. Cs. Horvàth and H. J. Lin, *J. Chromatogr., 149*, 43 (1978).
18. D. M. Ruthven and C. B. Ching, in G. Ganestos and P. E. Barker (Eds.), *Preparative and Production Scale Chromatography*, Dekker, New York, NY, 1993.
19. J. Bear, *Dynamics of Fluid in Porous Media*, Dover, New York, NY, 1988.
20. R. M. Nicoud and A. Seidel-Morgenstern, "Adsorption Isotherms: Experimental Determination and Application to Preparative Chromatography," *Isol. Purif. 2*, 165–200 (1996).
21. M. Mazzotti, G. Storti, and M. Morbidelli, "Robust Design of Countercurrent Adsorption Separation: 3. Nonstochiometric System," *AIChE J., 42*, 2784–2796 (1996).
22. M. Mazzotti, G. Storti, and M. Morbidelli, "Optimal Operation of Simulated Moving Bed Units for Nonlinear Chromatographic Separations," *J. Chromatogr. A, 769*, 3–24 (1997).
23. R. M. Nicoud, "The Simulated Moving Bed: A Powerful Chromatographic Process," *LC-GC Int., 5*, 43–47 (1992).
24. G. Guiochon, S. Golshan-Shirazi, and A. Katti, *Fundamentals of Preparative and Nonlinear Chromatography*, Academic Press, Boston, MA, 1994.
25. D. Tondeur and M. Bailly, "Simulated Countercurrent, Fixed Bed and Column Switching schemes," in R. M. Nicoud (Ed.), *Simulated Moving Bed: Basics and Applications*, INPL, Nancy, 1993 pp. 95–117.
26. G. Biressi, O. Ludemann-Hombourger, R. M. Nicoud, and M. Morbidelli, "Design and Optimisation of a Simulated Moving Bed Unit: Role of Deviations from Equilibrium Theory," *J. Chromatogr. A.*, Submitted for Publication.

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