Production Rate of an Isotachic Train in Displacement Chromatography

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The shock layer theory permits the derivation of an equation relating the thickness of the shock layer or mixed zone between successive bands in a fully developed isotachic train and the experimental parameters (mobile-phase flow velocity, concentration and retention factor of the displacer, column length, and average particle size of the packing material). It also permits the calculation of the amount of each product contained in this mixed zone. The main assumptions made are the use of the competitive Langmuir isotherm, the identity of axial dispersion coefficients, and the mass-transfer rate constants for different components. These equations make it possible to calculate the production rate and recovery yield achieved with an isotachic train, and to optimize the experimental conditions for maximum production rate. The shock layer thickness increases rapidly and the production rate decreases sharply when $\alpha - 1$ *tends toward 0. In agreement with previous experimental results, there are well defined optimum flow velocity and displacer concentrations which vary depending on feed components. This theory permits an easy access to the optimization of these parameters.*

Introduction

Displacement is a mode of chromatography in which the injection of a sample pulse is immediately followed by a change in the mobile phase composition. Before injection, the column is filled with a carrier mobile phase in which the sample components are more or less strongly retained by the stationary phase. Upon completion of the injection, this stream is replaced by a stream of a solution of a displacer, a compound which is more strongly retained than any sample component (Tiselius, 1943). Displacement differs from step gradient chromatography in the nature of the interaction of the mobile phase with the stationary phase, the distinction being especially important in reversed phase or hydrophobic interaction chromatography. In step gradient chromatography, the stream of carrier is replaced by a stream of a solution of a strong solvent in which the sample components are still retained. These components elute after the breakthrough front of the strong solvent. The theory of displacement chromatography has been studied in detail by Glueckauf (1946), Helfferich and Klein (1970), and Rhee et al. (1982), all using the ideal model of chromatography. More realistic models have been used, but so far only for the numerical solutions which they provide (Golshan-Shirazi and Guiochon, 1989; Phillips et al., 1989; Yu and Wang, 1989), and which permit systematic calculations (Katti and Guiochon, 1988). The results of these calculations suggest that there are still some unsolved theoretical problems in displacement chromatography.

All common concepts used in this area are based on the theoretical work done with the ideal model (Glueckauf, 1946; Helfferich and Klein, 1970; Rhee et al., 1982), and on the assumption of the full development of an isotachic train (Horváth et al., 1981; Frenz and Horvath, 1988). Unfortunately, actual columns have a finite efficiency, and real displacement chromatograms exhibit a few features which are not in agreement with this common wisdom (Katti and Guiochon, 1988). Of particular concerns are the lack of interest given to the mixed bands between successive zones, which are quite important (Katti and Guiochon, 1988), the drastic limitations of any optimization procedure based on the use of the ideal model (Jen and Pinto, 1992), the apparent lack of relationship between the separation factor and the actual difficulty of the separation, and finally, the practical difficulties encountered

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in achieving an isotachic train. All these difficulties are related to the success of the conceptual explanations derived from the ideal model, and the reluctance of the culture to accept the more sophisticated results derived from realistic models of chromatography.

For example, it has long been known in elution chromatography that the column efficiency depends on the mobile phase velocity, and that there is an optimum value of this velocity for which the relative bandwidth under experimental conditions of linear chromatography is minimum. There has been no such study regarding the width of the mixed zones in displacement chromatography. Frenz et al. (1985), however, have shown that there is an optimum velocity for maximum production rate. This result has been demonstrated by Katti et al. (1991), using systematic calculations of the optimum experimental conditions. Similarly, it is a classical result in analytical chromatography that the column efficiency required to separate two components with a certain degree of resolution is proportional to $[\alpha/(\alpha-1)]^2$ (Purnell, 1960). It has been shown on the basis of theoretical discussions (Golshan-Shirazi and Guiochon, 1989) and confirmed by numerical calculations (Felinger and Guiochon, 1992a) that the production rate in preparative chromatography by overloaded elution is approximately to $[(\alpha-1)/\alpha]^a$, with a close to 3 at low α values, and becoming smaller when α increases above 1.2. Similar calculations have lead Felinger and Guiochon (1992b) to the same conclusions for displacement. There are no theoretical discussions of this problem in the literature, nor any systematic experimental investigations, except for some limited results by Frenz et al. (1985, 1988). At present, all these facts coexist without being organized into a logical framework.

Obviously, since the isotachic train propagates unchanged, the maximum production rate is achieved for experimental conditions which correspond to a not yet fully developed train (Jen and Pinto, 1992; Katti et al., 1991; Felinger and Guiochon, 1992). On the other hand, the recovery yield will be maximum when this train is developed. The recovery yield under conditions of maximum production rate can be unacceptably low (Felinger and Guiochon, 1992). This justifies the investigation of the properties of the isotachic train from a practical point of view.

The shock layer theory developed by Rhee and Amundson (1972, 1974) and Rhee et al. (1989) is the tool needed for the investigation of the properties of the mixed zones between successive bands in the isotachic train. It has been used previously for the study of the thickness of the front shock layer of breakthrough curves (Zhu et al., 1993a), and of the two shock layers in binary frontal analysis (Ma and Guiochon, 1992). The objective of this article is the study of the optimization of the experimental conditions in displacement chromatography with isotachic train, based on the use of the shock layer theory.

Theory

We present first a brief summary of the shock layer theory as developed by Rhee and Amundson (1972, 1974) and Rhee et al. (1989). Then, we use the equations they have derived, and which give the concentration profile in the shock layer, to calculate the areas of the shock layers for one component (breakthrough curve) and between two components (isotachic train). These areas are proportional to the amount of material contained in them.

The shock layer theory is based on the use of the simple kinetic model of chromatography (Golshan-Shirazi and Guiochon, 1992), in which the contributions to band broadening by axial dispersion (that is, molecular diffusion, packing tortuosity, and eddy diffusion) are lumped in an axial dispersion coefficient D_L, and the contributions of the kinetics of the different mass-transfer processes and of adsorption/desorption are lumped into a single rate constant k_f. The band profiles are given by the following system of partial differential equations, written in dimensionless coordinates:

$$\frac{\partial C_i}{\partial \tau} + F\frac{\partial q_i}{\partial \tau} + \frac{\partial q_i}{\partial \chi} = \frac{1}{Pe}\frac{\partial^2 C_i}{\partial \chi^2} \tag{1}$$

$$\frac{\partial q_i}{\partial \tau} = St[f(C_1, C_2, \ldots, C_i, C_{i+1}, \ldots) - q_i] \tag{2}$$

Equation 1 is the mass balance equation of component i, and Eq. 2 the kinetic equation based on the solid film linear driving force model. The function $f(C_1, \ldots, C_i, \ldots)$ is the equilibrium isotherm. In keeping with the assumptions of the shock layer theory, the Peclet and Stanton number are assumed to be identical for the two components involved in a shock layer, that is, for all the components in the isotachic train; more on the practical limitations of this assumption later. The system of Eqs. 1 and 2 is completed with an initial condition (column empty) and the boundary conditions of displacement (Rhee and Amundson, 1974).

Shock layer thickness in displacement chromatography

Cooney and Lightfoot (1965) have shown that the system of Eqs. 1 and 2 has an asymptotic solution in the case of a single component. This result was extended to a multicomponent system by Cooney and Strusi (1972). Rhee and Amundson (1972, 1974) showed that it is possible to define and calculate the thickness of the profile in this asymptotic solution. Their definition of the shock layer thickness in the cases of a breakthrough curve and of a binary system are illustrated in Figures 1a and 1b, respectively.

First, they demonstrated that the concentration profiles of either one of two components in the shock layer between two constant states in a mixed zone are solutions of the following differential equation:

$$-\frac{\lambda}{PeSt}\frac{d^2C_i}{d\xi^2} + \left[\frac{1}{Pe} + \frac{\lambda(1-\lambda)}{St}\right]\frac{dC_i}{d\xi} = \lambda F \mathcal{F}(C_i, C_{p,i}, C_{i+1}, C_{p,i+1}) \tag{3}$$

where $\xi = \chi - \lambda\tau$, i is the rank of the component in the train, between 1 and n, and the function $\mathcal{F}(C_i, C_{p,i}, C_{i+1}, C_{p,i+1})$ depends on the parameters of the competitive isotherm (more on this function later). λ is the dimensionless velocity of the shock layer; in the case of an isotachic train, it is the velocity of the breakthrough curve of the displacer. In Eq. 3 the mass-transfer kinetics and the axial dispersion appear to play symmetrical roles. They are coupled through the second differential, and so cannot be considered independently. Thus, in the general case, Eq. 3 has no analytical solutions.

There is an analytical solution, however, when either *Pe* is infinite ($D_L = 0$, no axial dispersion) or *St* is infinite ($k_f = \infty$, infinitely fast mass-transfer kinetics). In practice, since the product $PeSt = k_f L^2/D_L$ is very large, almost always in excess of 1×10^6, the solution obtained by neglecting the first term in Eq. 3 is an excellent approximation (Rhee and Amundson, 1974).

Using Eq. 3, Rhee and Amundson derived a relationship between the shock layer thickness (SLT) and the experimental parameters. This equation contains an integral which depends on $\mathfrak{F}(C, C_0^l, C_0^r)$ and is a function of the equilibrium isotherm. It is apparently quite complex, but it is easily calculated when using the Langmuir competitive isotherm model:

$$q_i = \frac{q_s \Gamma_i}{1 + \Gamma_1 + \Gamma_2} \tag{4}$$

with $\Gamma_i = b_i C_i$. With the Langmuir isotherm, the hodograph transform of the concentration profiles of the two components in the shock layer is a straight line, which leads to a great simplification. When the calculation is carried out, a surprisingly simple relationship is obtained for the shock layer thickness (Zhu and Guiochon, 1993). Depending on the dimension chosen for the SLT, it is given by one of the following three equations:

$$\Delta\xi = \frac{1 + K_d}{K_d} \left[\frac{D_L}{uL} + \frac{K_d u}{(1 + K_d)^2 k_f L} \right] \frac{\alpha + 1}{\alpha - 1} \ln \left| \frac{1 - \theta}{\theta} \right| \tag{5a}$$

$$\Delta\eta_x = \left[\frac{D_L (1 + K_d)}{K_d u} + \frac{u}{(1 + K_d) k_f} \right] \frac{\alpha + 1}{\alpha - 1} \ln \left| \frac{1 - \theta}{\theta} \right| \tag{5b}$$

$$\Delta\eta_t = \left[\frac{D_L (1 + K_d)^2}{K_d u^2} + \frac{1}{k_f} \right] \frac{\alpha + 1}{\alpha - 1} \ln \left| \frac{1 - \theta}{\theta} \right| \tag{5c}$$

where $\Delta\xi$, $\Delta\eta_x$ and $\Delta\eta_t$ are the SLT in dimensionless coordinates, space and time units, respectively, with:

$$K_d = \frac{k'_{0,d}}{1 + \Gamma_d} \tag{5d}$$

and

$$\Delta\eta_x = L \Delta\xi \tag{6a}$$

$$\Delta\eta_t = \frac{L}{U_{sd}} \Delta\xi \tag{6b}$$

$$U_{Sd} = \frac{u}{1 + K_d} \tag{6c}$$

where L is the column length, and U_{Sd} the velocity of the displacer breakthrough front.

The amount of material contained in the mixed zone is equal to the area of the shock layer. Although the width of the shock layer is the same for the two components, these areas will of course, be different, since the two constant states are different. The dimensionless area of a shock layer is given by:

$$S = \int_{\xi^r_*}^{\xi^{l*}} \Gamma_i d\xi \tag{7}$$

$d\xi$ can be derived from Eq. 3. However, the calculation is slightly different for the front shock layer of the first component band and for the shock layers between successive bands in the isotachic train.

Area of a single component shock layer

A single component shock layer is illustrated in Figure 1a. This is the case of a breakthrough curve, or of the first component in an isotachic train. We consider a positive concentration step moving along the column. The low concentration is on the exit side of the column and exits first. The high concentration is on the inlet side and exits last.

If we neglect the first term of Eq. 3, the profile of the asymptotic solution is given by the following simplified differential equation (Rhee and Amundson, 1972):

$$\left(\frac{1}{Pe} + \frac{\lambda(1 - \lambda)}{St} \right) \frac{dC}{d\xi} = \lambda F \mathfrak{F}(\mathrm{C}, C_0^l, C_0^r)$$
$$= \lambda F \frac{f(C_0^r) - f(C_0^l)}{C_0^r - C_0^l} (C - C_0^l) - f(C) + f(C_0^l) \tag{8}$$

where the superscripts *l* and *r* refer to the left and right sides of the shock layer, with the convention that the shock layer moves from right to left. In the case of the first component of the isotachic train, the initial concentration is $C_0^r = C_{10} = 0$, and $f(C_0^r) = 0$. Its final concentration is the plateau concentration, $C_0^l = C_{p,1}$. If the isotachic train is formed, all the shock layer velocities are the same as the velocity of the displacer breakthrough front, hence:

$$\lambda_i = \lambda_d \tag{9a}$$

$$K_i = K_d \tag{9b}$$

$$C_{p,i} = \frac{1}{b_i} \left[\frac{a_i}{a_d} (1 + \Gamma_d) - 1 \right] \tag{9c}$$

Equation 9c is derived from Eqs. 4 and 9b. When the competitive Langmuir isotherm model applies, the column saturation capacity is the same for all components, $q_s = a_i/b_i = a_d/b_d$ hence $a_i/a_d = b_i/b_d$. Finally,

$$\mathfrak{F}(C, C_0^l, C_0^r) = \frac{q_{p1}}{C_{p,1}} C_1 - q_1 = q_s \Gamma_1 \left(\frac{1}{1 + \Gamma_{p1}} - \frac{1}{1 + \Gamma_1} \right) \tag{10}$$

Combining Eqs. 8 and 10, and solving for $d\xi$ gives:

$$d\xi = \frac{1}{\lambda F a_1} \frac{\dfrac{1}{Pe} + \dfrac{\lambda(1 - \lambda)}{St}}{\Gamma_1 \left(\dfrac{1}{1 + \Gamma_{p1}} - \dfrac{1}{1 + \Gamma_1} \right)} d\Gamma_1 \tag{11}$$

Combination of Eqs. 7 and 11 gives:

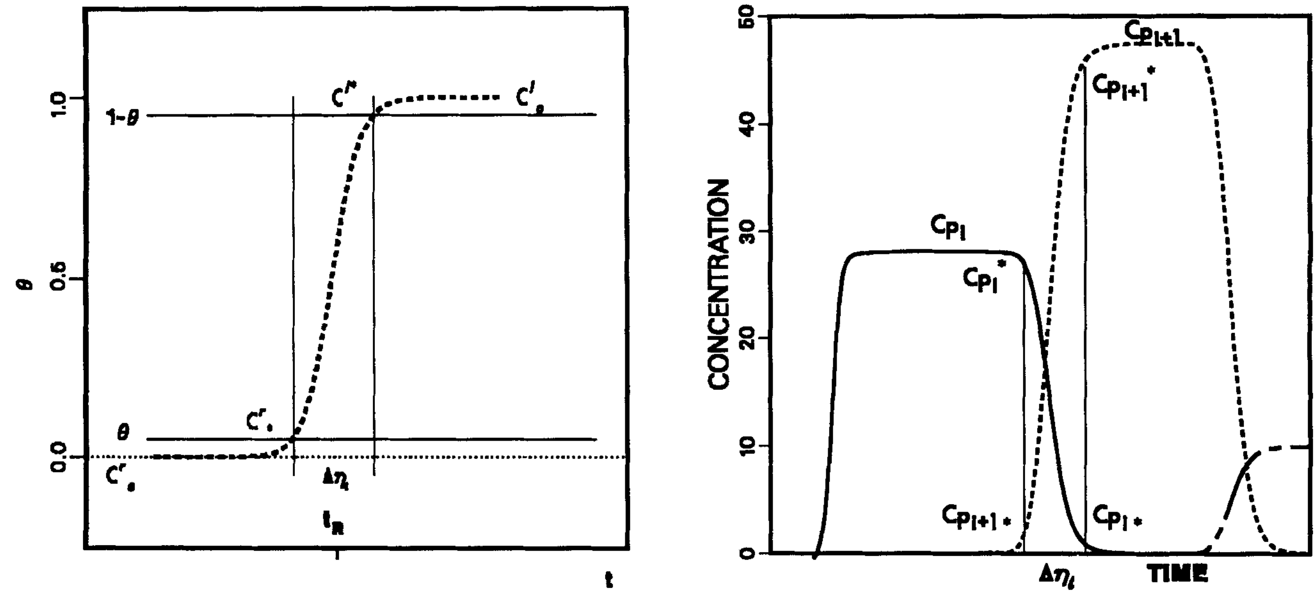

Figure 1. Definition of the shock layer parameters.

(a) Shock layer of a single component; (b) shock layer between two components.

$$S=\frac{\frac{1}{Pe}+\frac{\lambda(1-\lambda)}{St}}{\lambda k_1'}\int_{\Gamma^r_{1*}}^{\Gamma^{l*}_1}\frac{(1+\Gamma_{p1})(1+\Gamma_1)}{\Gamma_{p1}-\Gamma_1}\,d\Gamma_1 \tag{12a}$$

$$=\frac{\frac{1}{Pe}+\frac{\lambda(1-\lambda)}{St}}{\lambda k_1'}(1+\Gamma_{p1})\left[\Gamma_{p1}+(1+\Gamma_{p1})\ln\frac{\Gamma^{r*}-\Gamma_{p1}}{\Gamma^l_*-\Gamma_{p1}}\right] \tag{12b}$$

where $k_1'=Fb_1q_s$ is the retention factor of the component, $\Gamma^r_*=\theta\Gamma_{p1}$ and $\Gamma^{l*}=(1-\theta)\Gamma_{p1}$ (see Figure 1a). Replacing the dimensionless parameters gives:

$$S=\frac{1+K_d}{K_d}\left[\frac{D_L}{Lu}+\frac{K_du}{(1+K_d)^2Lk_f}\right]\times\left[(2\theta-1)\Gamma_{p1}+(1+\Gamma_{p1})\ln\frac{1-\theta}{\theta}\right] \tag{13}$$

Note that $K_d=K_1(C_{p,1})$ (Eq. 9b) is the isotachic condition and leads to the value of the concentration plateau, $C_{p,1}$ (Eq. 9c).

For the sake of simplicity in the following relationships and in the discussion, let:

$$\hat{F}(\theta,\Gamma_{p1})=(2\theta-1)\Gamma_{p1}+(1+\Gamma_{p1})\ln\frac{1-\theta}{\theta} \tag{14a}$$

$$\hat{\Phi}^d=\frac{D_L(1+K_d)}{K_dLu}+\frac{u}{Lk_f} \tag{14b}$$

$$\hat{\Phi}^x=\frac{D_L(1+K_d)}{K_du}+\frac{u}{k_f} \tag{14c}$$

$$\hat{\Phi}^t=\frac{D_L(1+K_d)^2}{K_du^2}+\frac{1}{k_f} \tag{14d}$$

Then the area of the front shock layer in frontal analysis is given by one of the following equations, depending on the unit:

$$S^d=\hat{\Phi}_d\hat{F}(\theta,\Gamma_{p1}) \tag{15a}$$

$$S^x=\frac{\hat{\Phi}^x}{b_1}\hat{F}(\theta,\Gamma_{p1}) \tag{15b}$$

$$S^t=\frac{\hat{\Phi}^t}{b_1}\hat{F}(\theta,\Gamma_{p1}) \tag{15c}$$

Note that in preparative chromatography the collection of the front shock layer of the first band has as only drawbacks the possible collection of the early eluting impurities, since impurities accumulate in shock layers (Zhu et al., 1991), and a dilution of the purified fraction.

Shock layer area in displacement chromatography

In displacement chromatography, the shock layer involves two components. Figure 1b illustrate the profiles of the two components in the mixed zone. Each band after the first one has a shock layer on each side. The superscripts f and r are used to denote the corresponding parameters. We consider first the shock layer between components i and $i+1$, which is a rear shock layer for component i and a front shock layer for component $i+1$. If we neglect the first term of Eq. 3, as suggested by Rhee and Amundson (1974), the profile of the asymptotic solution is given by the following differential equation:

$$\left(\frac{1}{Pe}+\frac{\lambda(1-\lambda)}{St}\right)\frac{dC_i}{d\xi}=\lambda F\mathfrak{F}(C_i,C_{p,i},C_{i+1},C_{p,i+1}) \tag{16}$$

Using the hodograph transform of the band profiles of the components i and $i+1$ in the mixed zone, Rhee and Amundson (1974) have shown that a plot of C_{i+1} vs. C_i is a straight line if the competitive isotherm is given by the Langmuir model, and if the two components have the same apparent dispersion coefficient and the same mass-transfer kinetics rate constant. The equation of this straight line is:

$$\frac{C_i}{C_{p,i}}+\frac{C_{i+1}}{C_{p,i+1}}-1=0 \tag{17a}$$

$$C_i=C_{p,i}-\frac{C_{p,i}}{C_{p,i+1}}\,C_{i+1} \tag{17b}$$

$$C_{i+1}=C_{p,i+1}-\frac{C_{p,i+1}}{C_{p,i}}\,C_i \tag{17c}$$

where $C_{p,i}$ is the plateau concentration of component i in the isotachic train. Rhee and Amundson have shown that this property permits the decoupling of the competitive isotherm (1974). The concentration profiles of the two components in the shock layer are given by the same equations as the concentration profile of a single component breakthrough curve, provided that we replace the coefficients of the single component Langmuir isotherm model used by the values obtained by combining Eqs. 4 and 17. This decouples the competitive isotherm into two single component isotherms. Obviously, the coefficients of the decoupled isotherms of the two components are different. We derive here the coefficients of component i in its front and rear shock layers.

For the front of the band of component i, we use Eq. 17 written for component $i-1$, and the competitive isotherm of i becomes:

$$q_i=\frac{q_s b_i C_i}{1+b_{i-1}C_{p,i-1}+C_i\left[b_1-b_{i-1}\,\frac{C_{p,i-1}}{C_{p,i}}\right]} \tag{18}$$

Hence,

$$A_i^f=\frac{b_i q_s}{1+b_{i-1}C_{p,i-1}} \tag{19a}$$

$$B_i^f=\frac{b_i-b_{i-1}\,\dfrac{C_{p,i-1}}{C_{p,i}}}{1+b_{i-1}C_{p,i-1}}=\frac{\alpha_{i-1,i}-1}{C_{p,i}} \tag{19b}$$

The second Eq. 19b is obtained by using Eq. 9c. Similarly, eliminating C_{i+1} between Eqs. 4 and 17 gives the decoupled coefficients for the rear of the i band in the isotachic train. The result can be simplified by combination with Eq. 9c. Finally:

$$A_i^r=\frac{b_i q_s}{1+b_{i+1}C_{p,i+1}} \tag{20a}$$

$$B_i^r=\frac{b_i-b_{i+1}\,\dfrac{C_{p,i+1}}{C_{p,i}}}{1+b_{i+1}C_{p,i+1}}=\frac{1-\alpha_{i,i+1}}{\alpha_{i,i+1}C_{p,i}} \tag{20b}$$

$$B_i^f=\frac{\alpha_{i-1,i}-1}{C_{p,i}} \tag{20c}$$

Because the competitive isotherm is decoupled, the function $\mathfrak{F}(C_i, C_{p,i}, C_{i+1}, C_{p,i+1})$ can also be decoupled into two separate, independent functions $\mathfrak{F}_i(C_i, C_{p,i}, C_{p,i+1})$ and $\mathfrak{F}_{i+1}(C_{i+1}, C_{p,i}, C_{p,i+1})$ which are given by the same relationship as in Eq. 8, but using the coefficients in Eqs. 19a to 20b:

$$\mathfrak{F}_i(C_i, C_{p,i}, C_{p,i+1})=\frac{F(0)-F(C_{p,i})}{0-C_{p,i}}\,(C_i-C_{p,i})-F(C_i)+F(C_{p,i}) \tag{21}$$

with $F(C_i)=A_iC_i/(1+B_iC_i)$. Thus, we can calculate the area of the shock layer or mixed zone between components i and $i+1$ by using the same equations as for the calculation of the area of the single component shock layer. The result is

$$S_i^d=\hat{\Phi}^d\hat{F}(\theta,\,\alpha) \tag{22a}$$

$$S_i^x=\frac{\overline{\Phi}^x}{B_i}\,\hat{F}(\theta,\,\alpha) \tag{22b}$$

$$S_i^t=\frac{\overline{\Phi}^t}{B_i}\,\hat{F}(\theta,\,\alpha) \tag{22c}$$

with

$$\hat{F}_i^f(\theta,\,\alpha_{i-1,i})=(2\theta-1)(\alpha_{i-1,i}-1)+\alpha_{i-1,i}\ln\frac{1-\theta}{\theta} \tag{23a}$$

$$\hat{F}_i^r(\theta,\,\alpha_{i,i+1})=(2\theta-1)\,\frac{1-\alpha_{i,i+1}}{\alpha_{i,i+1}}+\frac{1}{\alpha_{i,i+1}}\ln\frac{1-\theta}{\theta} \tag{23b}$$

$$\hat{\Phi}_d^d=\frac{D_L(1+K_d)}{K_dLu}+\frac{u}{Lk_f} \tag{23c}$$

$$\hat{\Phi}_d^x=\frac{D_L(1+K_d)}{K_du}+\frac{u}{k_f} \tag{23d}$$

$$\hat{\Phi}_d^t=\frac{D_L(1+K_d)^2}{K_du^2}+\frac{1}{k_f} \tag{23e}$$

In Eqs. 22b and 22c, B_i^f is associated with $\hat{F}_i^f$ and B_i^r with $\hat{F}_i^r$.

Production rate under isotachic train conditions

There is a major difficulty in defining the production rate in displacement chromatography. It is most difficult to estimate properly the time required for column regeneration, because this time depends much on the particulars of the specific case studied. In some cases (such as in reversed phase chromatography), it will suffice to wash the column with a column volume of a strong eluent followed by a few column volumes of carrier for reequilibration. In other cases 50 to 100 column volumes of carrier solution may be needed. This difficulty could prevent a definitive comparison between elution and displacement chromatography. However, under experimental conditions separately optimized for the two methods (that is, using different columns), the production rate of the former method is nearly always higher than that of the latter, assuming that the regeneration time is negligible (Felinger and Guiochon, 1992a,b, 1993). Katti et al. (1991) optimized the same column successively for both methods and found comparable production rates, again neglecting the regeneration time. Note that all these authors found that the maximum production rate is achieved for nonisotachic conditions.

In the present case, since we want to optimize the experimental conditions under which an isotachic train is achieved, it is rather inconsequential to neglect the regeneration time which may depend somewhat on the retention factor of the displacer, but is little influenced by the displacer concentration and is independent of the other experimental conditions. We define the production rate as:

$$\mathcal{P}\nabla = \frac{\text{Amount of purified product collected}}{\text{Time needed to conduct the separation}} \tag{24}$$

The time needed to conduct the separation is the breakthrough time of the displacer, L/U_{Sd} (Eq. 6c). The amount of purified product collected is the amount injected minus the amount contained in the two mixed zones, that is, in the two shock layers, before and after the band. Thus:

$$\mathcal{P}\nabla = \frac{M - F_v(S_i^{f,t} + S_i^{r,t})}{L/U_{Sd}} = \frac{S\epsilon}{L(1+K_d)} \left\{ \frac{C_i^0 V_s u}{\epsilon S} - \left[\frac{\hat{F}_i^f(\theta,\ \alpha_{i-1,i})}{B_i^f} + \frac{\hat{F}_i^r(\theta,\ \alpha_{i,i+1})}{B_i^r} \right] \left[\frac{D_L(1+K_d)^2}{K_d} + \frac{u^2}{k_f} \right] \right\} \tag{25}$$

Equation 25 contains only parameters which are easily accessible, the coefficients of the Langmuir isotherms of the components involved and of the displacer, the common dispersion coefficient and mass-transfer rate constant, the mobile phase flow velocity, the column length, its cross-section area and its total porosity. The production rate and the recovery yield achieved in displacement chromatography, under isotachic conditions, are thus easy to calculate and optimize. Obviously, however, this equation is not valid before the isotachic train is formed. Finally, note that Eq. 25 contains the column length. There is an ambiguity here that the shock layer theory cannot solve. The isotachic train is an asymptotic solution, and we do not know what is the column length which is required to achieve the "practical" formation of this train. Therefore, optimization of the column length is impossible.

Results and Discussion

Equation 25 does not contain the absolute retention of any component, except the displacer. Under isotachic conditions, all bands move at the velocity of the displacer front, and each band is forced to reach the corresponding plateau concentration, $C_{p,i}$, given by Eq. 9c. $C_{p,i}$ depends on the displacer concentration and on the separation factor, $\alpha_{i,d}$, between the component and the displacer, but not on the retention factor of either the component or the displacer. As a consequence, the production rate of one component can be optimized independently of the retention factors of the two components in the neighbor bands. In order to illustrate the discussion, we have calculated displacement chromatograms for a four component mixture. Figure 2 shows the chromatograms obtained at three different velocities. To eliminate the trivial effect of the change in time scale associated with the velocity change, the chromatograms are given as plots of concentration vs. *volume of mobile phase passed*. Similar calculations have also been done for much lower values of the retention factors of the feed components and the displacer (coefficients in Table 1). An isotachic train was easily obtained, albeit after a much longer migration distance. Both sets of results are presented later. The finite-difference algorithm previously described (Ma and Guiochon, 1991) was used for these calculations which took several hours in most cases.

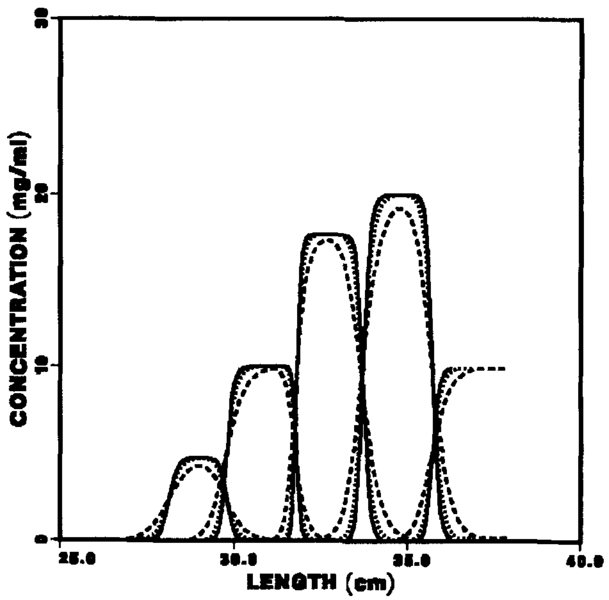

Figure 2. Displacement chromatogram of a four component feed.

Band profiles in an isotachic train calculated for three different flow velocities. Curve 1 (dotted line) 0.0033 cm/s; curve 2 (solid line) 0.0167 cm/s; curve 3 (chain line) 0.05 cm/s. $F=0.416$; $D_L=0.000023$ cm²/s; $k_f=0.33$ s^{-1}. Displacer concentration: 10 mg/mL. Langmuir isotherm coefficients in Table 1 (first set). $k'=Fa_i$.

Furthermore, it should be emphasized that, besides the displacer concentration and its retention factor, the dimensionless shock layer areas depend only on the coefficients D_a and k_f, and on the relative retention of the two successive components. These areas are independent of the isotherm coefficients. The actual areas in time or space units depend also on the coefficient B_i of the decoupled isotherm. Thus, this coefficient has some very important properties.

Table 1. Retention Factors of Two Sets of Components for the Calculations

First Set	*a*	*b*	Second Set	*a*	*b*
1	4	0.07	1	1.5	0.04
2	6	0.1	2	2.25	0.07
3	12	0.17	3	4.0	0.12
4	18	0.25	4	6.0	0.18
d	27	0.8	d	9.0	0.6

Properties of the coefficient B_i

The larger the coefficient B_i, the smaller the shock layer area and, accordingly, the higher the production rate. B_i depends on the displacer concentration and on the relative retention of the ith component to the displacer, through the dependence of the plateau concentration of the ith band on these parameters, as well as on the column saturation capacity, and on the separation factors of the two successive components and of the displacer and the ith component.

Combining Eqs. 20b (for components i and $i+1$) and Eq. 9c, and rearranging gives:

$$B_i^r = \frac{b_d b_i (b_i - b_{i+1})}{b_{i+1}[b_i(1 + b_d C_d) - b_d]} = \frac{1 - \alpha_{i,i+1}}{\alpha_{i,i+1} C_{p,i}} = \frac{b_i(1 - \alpha_{i,i+1})}{\alpha_{i,i+1}[\alpha_{d,i}(1 + b_d C_d) - 1]} \tag{26}$$

Since $\alpha_{i,i+1} = b_{i+1}/b_i$.

Influence of the Displacer Concentration. Rhee et al. (1982) have shown that there is a concentration threshold for the displacer, and that an isotachic train is possible only if the displacer concentration exceeds the watershed, that is, is such that:

$$C_d > C_d^* = \frac{b_d - b_i}{b_i b_d} = \frac{a_d - a_i}{a_i b_d} \tag{27a}$$

$$\Gamma_d > \Gamma_d^* = \alpha_{i,d} - 1 \tag{27b}$$

Thus, B_i^r is always negative when an isotachic train is formed, while B_i^f is positive. When the displacer concentration decreases towards C_d^*, B_i decreases towards $-\infty$, the shock layer area tends towards 0, and the recovery yield towards 100%. Unfortunately, this observation is of limited practical interest, because at the same time the plateau concentration of i tends towards 0, and both the column length and the time needed to achieve formation of the isotachic train increase indefinitely. As a consequence, the production rate tends towards 0.

Influence of the Separation Factor between Two Successive Components. The coefficient B_i increases with increasing separation factor of the two components i and $i+1$ or $i-1$ (Figure 3a). Thus, both the shock layer thickness and the shock layer area decrease with increasing $\alpha_{i,i\pm1}$. This is the expected consequence in displacement chromatography of the increased ease of the separation. We note, however, that the dependence of the actual importance of the shock layer on the separation factor is different for a front and a rear shock, and that, for a given value of the separation factor, the area of a rear shock layer is larger than the area of a front shock layer.

These theoretical results are well illustrated by a displacement chromatogram published by Horváth et al. (1983). This chromatogram (Figure 3b) illustrates the separation of inosine (I), deoxyinosine (DI), adenosine (A), and deoxyadenosine (DA). The plateau concentrations of the components of the first pair (I and DI) are nearly equal (within 5 to 10%), and the same is true for the second pair (A and DA). This shows that the concentrations of the intersection of the operating line and the isotherms of the two components of each pair are very close; hence, the separation factors of the two pairs are both close to unity. By contrast, the plateau concentration of A is nearly double that of DI. The thicknesses of the four binary shock layers are approximately (in mL) >0.4 (I-DI), <0.2 (DI-A), >0.6 (A-DA), and <0.1 (DA-d). This chromatogram demonstrates the relationship between separation factor and thickness of the mixed zones in displacement chromatography.

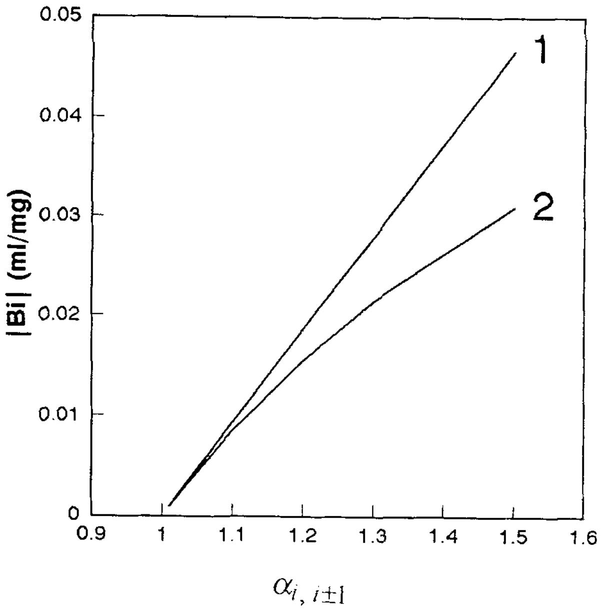

Figure 3a. Dependence of the decoupled Langmuir isotherm coefficient B_i on the separation factor $\alpha_{i,i\pm1}$.

Curve 1, front shock layer; curve 2, rear shock layer.

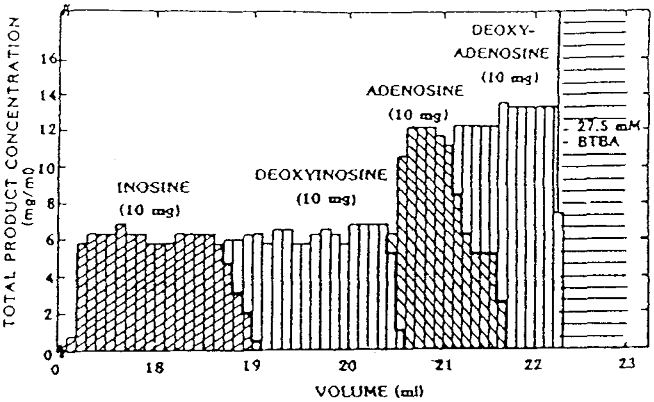

Figure 3b. Separation of inosine, deoxyinosine, adenosine and deoxyadenosine in displacement chromatography on Supelcosil LC-18.

Experimental results of Horvath et al. (1983). Reproduced with permission of Elsevier.

The production rate of a component i depends on the value of both separation factors, $\alpha_{i-1,i}$ and $\alpha_{i,i+1}$, with the components which are eluted before and after it in the isotachic train. Assuming these two factors to be equal, for the sake of simplicity, we calculate the production rate as a function of the common value, $\alpha_{i,i\pm1}$. Figure 4 shows how strong this dependence is on the separation factor.

Influence of the Separation Factor of the Displacer and the Component Studied. As seen above (Eq. 9c), in displacement

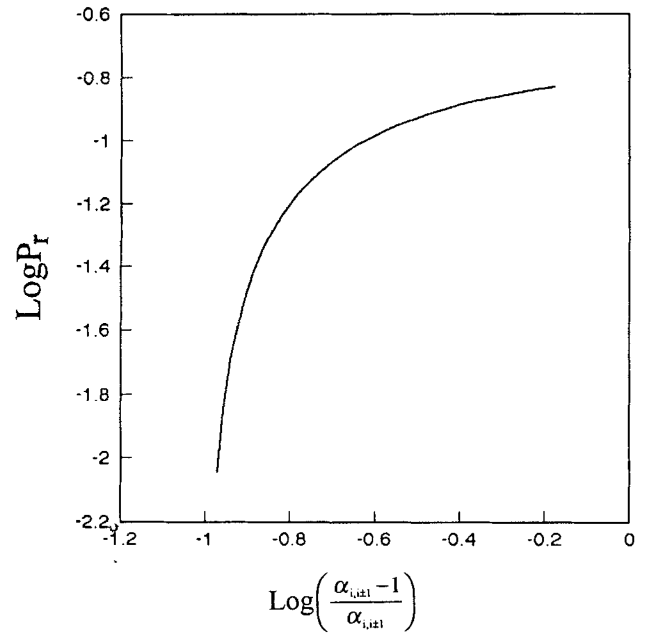

Figure 4. Plot of the production rate vs. $\alpha_{i,i\pm1}$, assuming $\alpha_{i,i+1}=\alpha_{i-1,i}=\alpha_{i,i\pm1}$.

Third component in Table 1 (second feed).

chromatography under isotachic conditions the retention of the displacer controls the band heights, which eliminates the direct influence of the retention factors of the feed components. The coefficient B_i, however, depends on the separation factor, $\alpha_{i,d}$, and increases almost linearly with increasing $\alpha_{i,d}$ (Figure 5). This implies that the recovery yield is improved by the choice of a strongly retained displacer. This explains why it is recommended to chose displacers which have a high retention factor (Frenz and Horváth, 1988). The production rate, however, depends on both $\alpha_{i,d}$ and k'_d. A compromise is needed and will be discussed below.

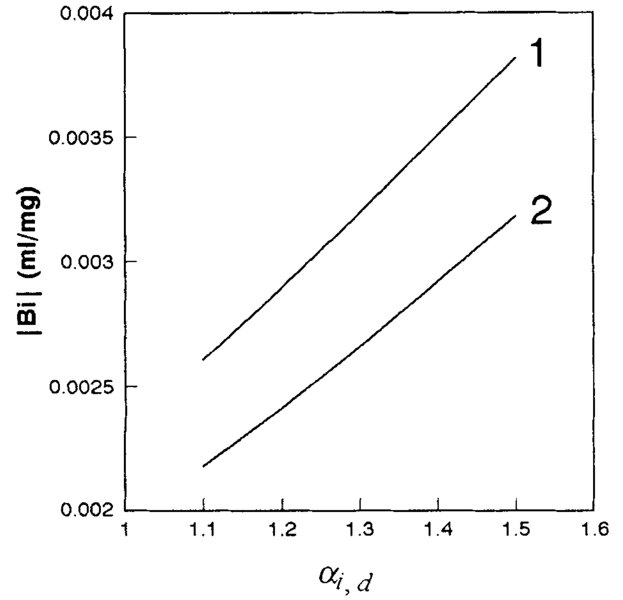

Figure 5. Dependence of the decoupled Langmuir isotherm coefficient B_i on the separation factor $\alpha_{i,d}$.

Curve 1, front shock layer; curve 2, rear shock layer. Third component in Table 1 (second feed).

Influence of the Column Saturation Capacity. According to the basic tenets of the competitive Langmuir isotherm model, the saturation capacity of the adsorbent, q_s, should be the same for all the components and for the displacer. Thus, Eq. 26 can be rewritten:

$$B_i^r=\frac{\dfrac{a_i}{q_s}\left(\dfrac{1}{\alpha_{i,i+1}}-1\right)}{\dfrac{1}{\alpha_{i,d}}\left(1+\dfrac{a_dC_d}{q_s}\right)-1} \tag{28}$$

Use of this equation permits the study of the influence of the saturation capacity on the production rate.

Optimum linear velocity of the mobile phase

Differentiation of Eq. 25 by respect to the mobile phase linear velocity permits the calculation of the optimum value of this velocity:

$$u_{\mathrm{opt}}^T=\frac{C_i^0V_sk_f}{2\epsilon S\left[\dfrac{\hat{F}_i^f(\theta,\ \alpha_{i-1,i})}{B_i^f}+\dfrac{\hat{F}_i^r(\theta,\ \alpha_{i,i+1})}{B_i^r}\right]} \tag{29}$$

The optimum velocity is proportional to the rate coefficient, k_f. It is independent of the absolute value of the retention factors, but depends on the isotherm parameters through the decoupled Langmuir isotherm coefficient B_i, as well as on the displacer concentration. Figures 6a and 6b illustrate the dependence of the production rate on the mobile phase velocity for two sets of four different components, one set corresponding to low values of the retention factors, the other to more conventional ones. The optimum velocity is different for the different components of the feed in a given isotachic train. It is much larger for the first component in the train because this component is involved in a single mixed zone.

Frenz et al. (1985) carried out a systematic investigation of the influence of the experimental conditions on the production rate of an isotachic train in displacement chromatography. They used as feed the hydrolysis products of methyl-furyl-butyrolactone. They reported that there is an optimum velocity for maximum production of purified fractions at a given degree of purity (Figure 6c). The general behavior of their experimental data is quite similar to the results of our model (cf. Figure 6a to 6c). Unfortunately, the limited adsorption isotherm data given by Frenz et al. (1985) do not permit the calculation of band profiles and the quantitative comparison between their experimental results and the results of the present theoretical analysis.

Optimum displacer concentration

The velocity of the isotachic train depends on both the mobile phase velocity and the displacer concentration (Eq. 6c). The latter determines the slope of the operating line, $q_d/C_d=$

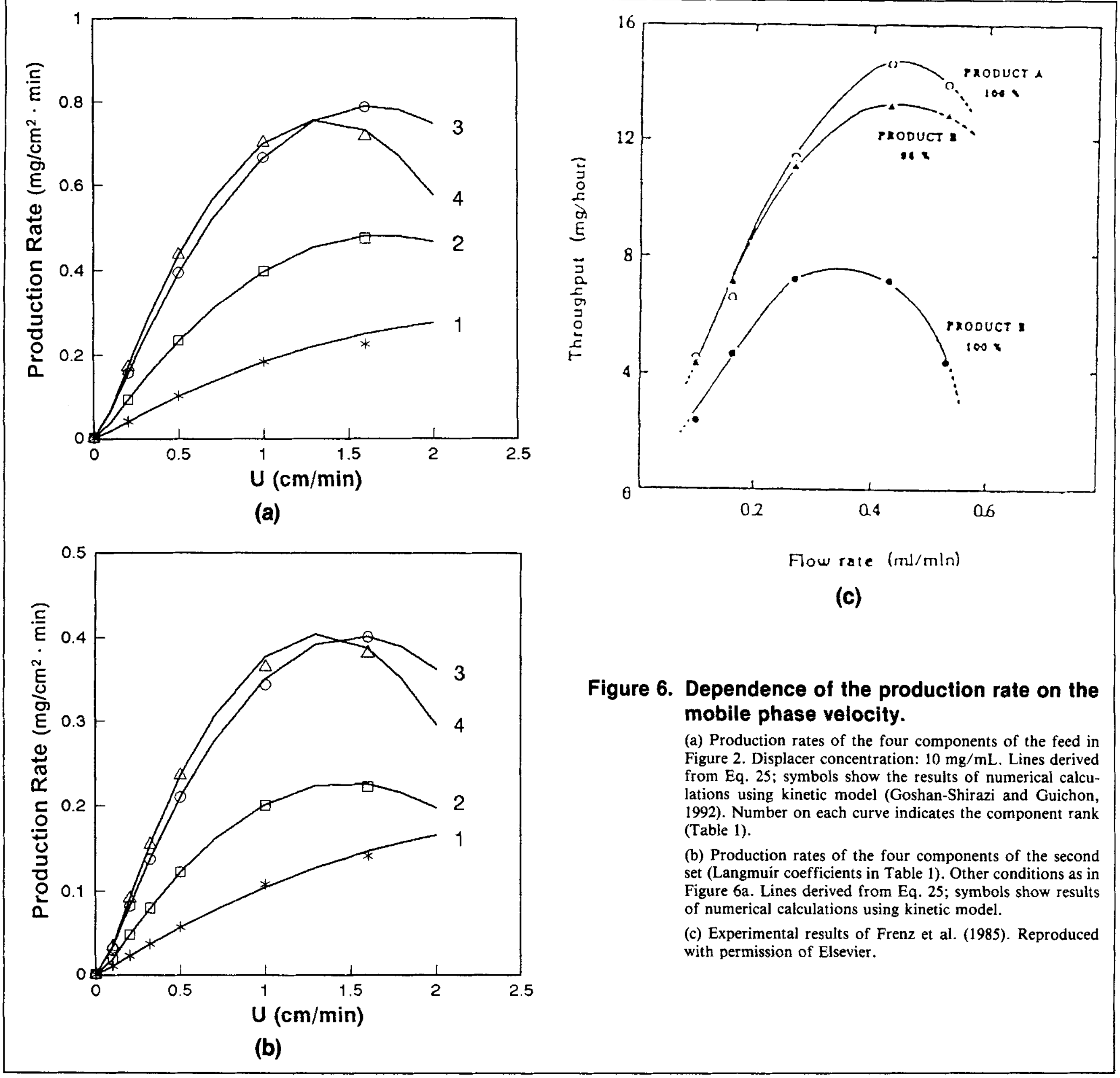

Figure 6. Dependence of the production rate on the mobile phase velocity.

(a) Production rates of the four components of the feed in Figure 2. Displacer concentration: 10 mg/mL. Lines derived from Eq. 25; symbols show the results of numerical calculations using kinetic model (Goshan-Shirazi and Guichon, 1992). Number on each curve indicates the component rank (Table 1).

(b) Production rates of the four components of the second set (Langmuir coefficients in Table 1). Other conditions as in Figure 6a. Lines derived from Eq. 25; symbols show results of numerical calculations using kinetic model.

(c) Experimental results of Frenz et al. (1985). Reproduced with permission of Elsevier.

K_d/F. Thus, it determines also the plateau concentrations of the bands of all the feed components (provided the condition in Eq. 27a is fulfilled, that is, that the slope of the operating line be smaller than the slope of the initial tangent to the isotherm). As there is an optimum mobile phase velocity, there is also an optimum displacer concentration. This latter optimum is easily calculated numerically, but an analytical solution is impossible since the differentiation of Eq. 25 by respect to C_d gives a fourth-degree algebraic equation which has no simple roots.

Figures 7a and 7b illustrate the dependence of the production rate of the two sets of four components on the displacer concentration. For each component, the curve starts at a symbol corresponding to the watershed concentration, the displacer concentration below which there is no displacement other than overloaded elution of the band. The watershed is the optimum concentration for the first component, and while it is barely lower than the optimum displacer concentration for the second component, it is much lower for the last two feed components.

In Figure 8 the experimental results obtained by Frenz et al. (1985) (Figure 8c) are compared with the results in Figures 7a and 7b. The experimental data are plots of the production rate vs. the normalized breakthrough time of the displacer. This time is defined as:

$$t_N=\frac{t_{R,d}-t_0}{t_0}=\frac{\dfrac{L}{U_{Sd}}-\dfrac{L}{u}}{\dfrac{L}{u}}=\frac{u}{U_{Sd}}-1=K_d \qquad (30)$$

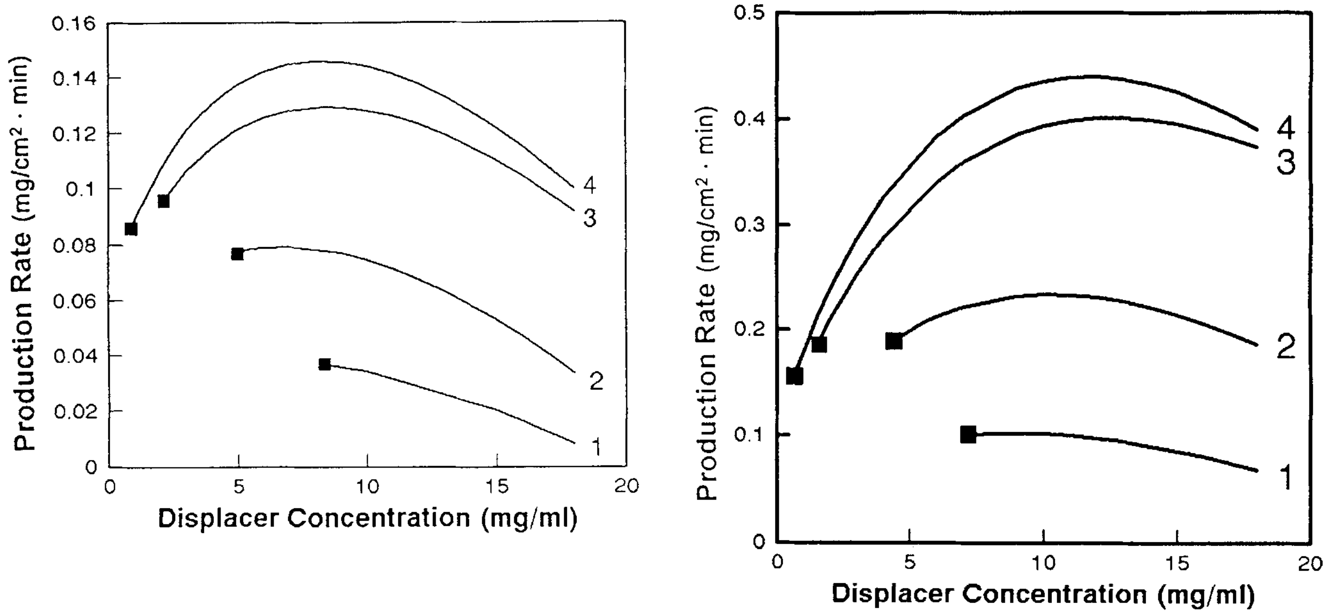

Figure 7. Dependence of the production rate on the displacer concentration.

(a) Production rate for the four components of the feed in Figure 2. Flow velocity: 0.05 cm/s. Lines derived from Eq. 25; the symbol on each line shows the watershed point; (b) same as Figure 7a, but for the four components of the second feed (Table 1). Number on each curve indicates the component rank (Table 1).

and K_d is proportional to $1/(1+b_dC_d)$ (Eq. 5d). The data in Figure 7 have been replotted as a function of K_d to facilitate the comparison. There is an excellent qualitative agreement between these two sets of results.

Optimum displacer retention factor

Differentiation of Eq. 25 by respect to k'_d permits the calculation of the optimum retention factor of the displacer, $k'_d = Fq_sb_d$. Again, numerical solutions only are possible. Figure 9 shows the dependence on k'_d of the production rate of the four components in Figure 2. In this case, we have assumed that when k'_d is changed, the retention factors of all the feed components are changed proportionally, the separation factors remaining constant (such as if $k'_{d,\mathrm{opt}}$ is 2.7, k'_4 becomes 1.8). The production rate increases rapidly with k'_d at first, goes through a maximum and decreases slowly with increasing k'_d at high values of this factor. The optimum value of the displacer retention factor is rather low in agreement with the results of a numerical study of the optimization of the experimental conditions in displacement chromatography (Felinger and Guiochon, 1993). This earlier study, which was not limited as the present one by the requirement of the development of an isotachic train at the column exit, reported that the optimum displacer retention factor was not much higher than the retention factor of the last component of the feed.

Conclusion

The critical parameters which control the production rate of a given component in displacement chromatography are the separation factors of that component and the two components which are immediately before and after it in the isotachic train, the column saturation capacity, the mobile phase velocity, and the displacer concentration. While the production rate increases rapidly and monotonically with $\alpha - 1$, there are optimum values of the mobile phase velocity, the displacer retention factor, and the displacer concentration. These optimum values are different for the different components of a given feed.

The dependence of the production rate on the retention factor of the displacer, or its separation factor with the main feed component, is more complex because this factor may also control the regeneration time. With the definition of the production rate used in this work, the production rate increases with increasing value of these parameters. The time required for the column regeneration also will increase, and experimental data are sorely lacking on this issue.

The validity of these results depends on the relevancy of the assumption that the rate constant of the lumped kinetic model, k_f, is the same for all the feed components and for the displacer, and that the axial dispersion coefficient, D_a, is also the same for all compounds. We have shown in a previous publication (Zhu and Guiochon, 1993b) that, when the value of k_f is different for two compounds, the thickness of the shock layer between their two bands is close to the average value of the thicknesses calculated with the two values of the rate constants. This result obtained with a ratio $k_{f,1}/k_{f,2}$ between 0.1 and 10 is certainly valid in most practical cases where the feed components are quite similar. It permits the extension of the present results to cases where the values of k_f and D_a are different. The essential limitation of the approach comes from the fact that the shock layer theory does not permit the optimization of the column length. Since the isotachic train is an asymptotic solution, we cannot calculate the column length required for its development.

Experimental results found in the literature agree well with the conclusions of this theoretical study (Frenz et al., 1985; Horváth et al., 1983), but this agreement remains qualitative. Experiments are in progress to assess the validity of the model. The choice between the present, analytical approach, and the

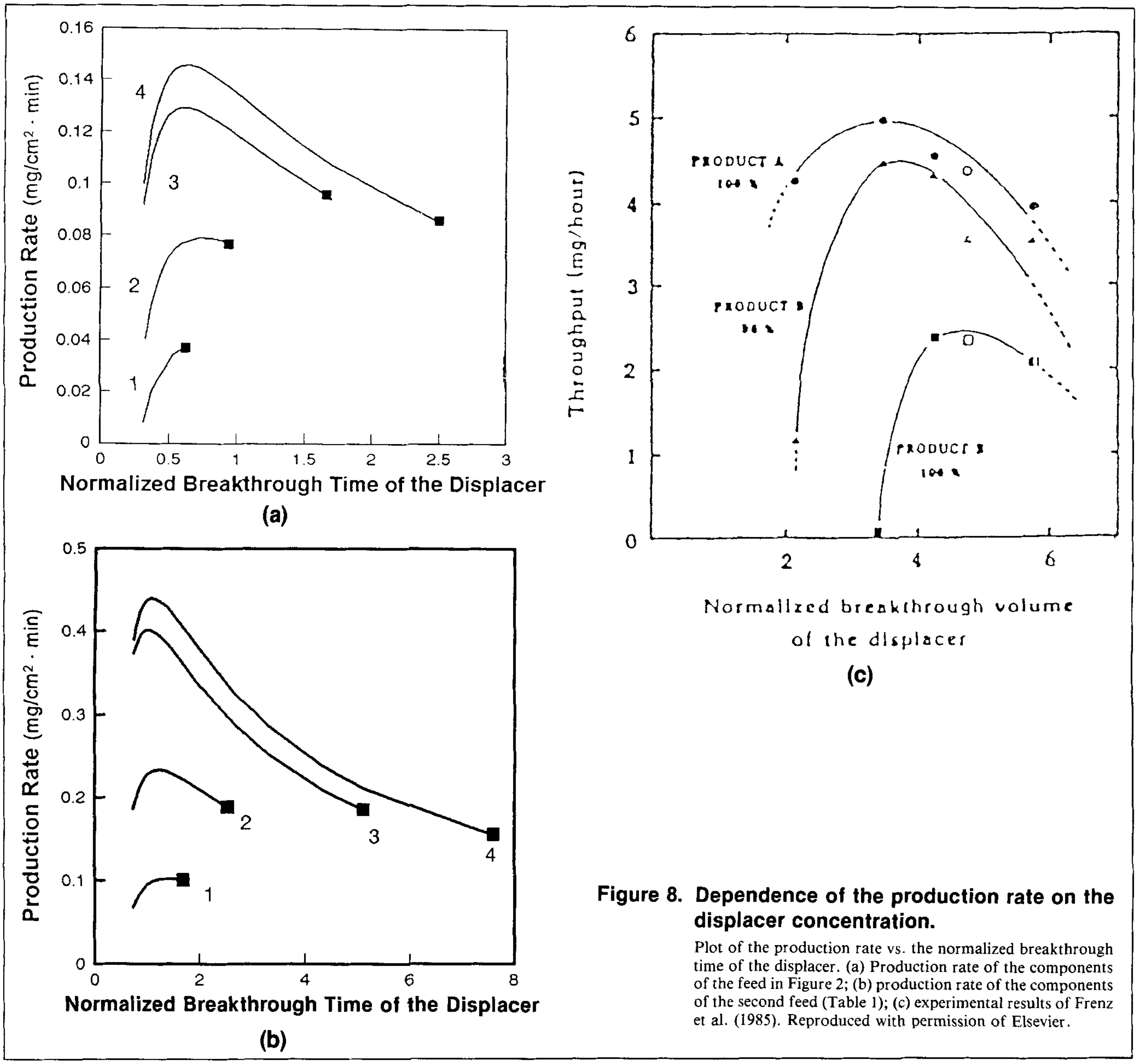

Figure 8. Dependence of the production rate on the displacer concentration.

Plot of the production rate vs. the normalized breakthrough time of the displacer. (a) Production rate of the components of the feed in Figure 2; (b) production rate of the components of the second feed (Table 1); (c) experimental results of Frenz et al. (1985). Reproduced with permission of Elsevier.

numerical method discussed previously (Katti et al., 1991; Felinger and Guiochon, 1992, 1993) depends on the process requirements. If the maximum production rate is required, the numerical approach permits the optimization of displacement chromatography under nonisotachic conditions. Then, however, the recovery yield may fall below 50%, and render the procedure uneconomical or otherwise unsatisfactory. If a high recovery yield is required, the approach presented here permits the optimization of the experimental conditions of an isotachic separation for maximum production rate, or for minimum solvent consumption if needed.

Acknowledgments

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Notation

b_i = coefficient in the Langmuir isotherm
C_i = concentration in the mobile phase
d_p = average particle diameter
$f(C_1, C_i, C_n)$ = competitive isotherm
$\mathfrak{F}$ = function in the differential equation giving the concentration profiles in a shock layer
F = phase ratio $[F=(1-\epsilon)/\epsilon]$
K_d = concentration dependent parameter in the shock layer equations $[K_d = k_d'/(1+\Gamma_d)]$
k_0' = retention factor at infinite dilution
Pe = Peclet number $(Pe = uL/D_m)$
q_i = concentration in the stationary phase
q_s = saturation capacity in the Langmuir isotherm
St = Stanton number $[St = (k_f L)/u]$
t = time
u = mobile-phase velocity
U_S = velocity of a shock or shock layer
z = distance along the column

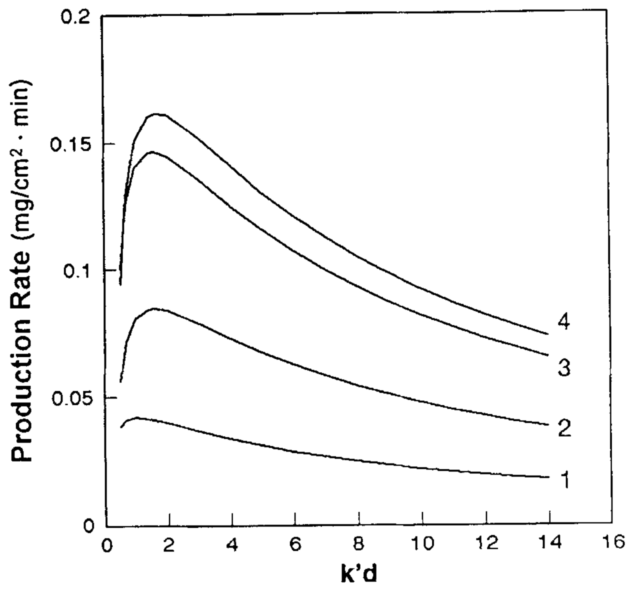

Figure 9. Dependence of the production rate on the retention factor of the displacer for the four components of the feed in Table 1 (second feed).

Flow velocity: 0.05 cm/s. Lines derived from Eq. 25. Number on each curve indicates the component rank (Table 1).

Greek letters

$\alpha_{i,j}$ = separation factor of components i and j [$\alpha_{i,j} = (k'_j/k'_i) = (b_j/b_i)$]
Γ_i = reduced concentration in the Langmuir isotherm ($\Gamma_i = b_i C_i$)
ϵ = total porosity of the column
θ = reduced concentration in a simple wave [$\theta = (C_i/C_i^0)$]
λ = shock and shock layer dimensionless velocity [$\lambda = [1/(1+K_d)]$]
ν = reduced velocity (particle Peclet number, $\nu = [(ud_p)/D_m]$
ξ = reduced coordinate ($\xi = \chi - \lambda\tau$)
τ = reduced time [$\tau = (tu/L)$]
χ = reduced space coordinate ($\chi = z/L$)

Superscripts

l = left side of the shock layer (before passage of the shock layer)
r = right side of the shock layer (after passage of the shock layer)
$*$ = high concentration at one end of a shock layer [$C^*_{p,i} = (1-\theta)C_{p,i}$]

Subscripts

d = displacer
i,j = components
p = plateau concentration in the isotachic train
$*$ = low concentration at one end of a shock layer ($C_{p,i*} = \theta C_{p,i}$)

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