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MATHEMATICAL MODELLING OF THE PEAK IN LIQUID CHROMATOGRAPHY

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SUMMARY

A program for the numerical solution of the transport differential equation describing the behaviour of a peak on a chromatographic column for an arbitrary shape of the equilibrium isotherm and an arbitrary amount injected for one- and two-component systems is presented. For one component, the influence of the axial dispersion coefficient, the separation coefficient, the curvature of the equilibrium isotherm and the apparatus function of the detector were examined. For a two-component system, the column overloading for pairs of components with various mutual influences was studied.

INTRODUCTION

Owing to the increasing availability of larger computers in chemical laboratories and the growing mathematical expertise of research chemists, mathematical modelling is an expanding technique. An exact mathematical model is a tool that permits both a deeper understanding of a process being studied and the optimization of parameters that influence this process, together with the prediction of results for arbitrary conditions. The development of the model is the first step in this procedure.

The fundamental mathematical description of the chromatographic process is based on the transport differential equation, defined for example by Deyl *et al.*[1] (see eqn. 1). Different approaches to the solution of this equation, leading to an analytical expression or to a numerical solution, can be found in the literature. The analytical solution for a linear equilibrium isotherm and a Dirac-shaped injected peak[2,3] is regarded as valuable. As follows from the relationship for reduced statistical moments[4], the axial dispersion coefficient D has a dominant influence on the width and asymmetry of a peak. The analytical solution considering the axial dispersion and non-linear equilibrium isotherms, approximated by a second-order polynomial, were demonstrated by Jaulman and co-workers[5,6], including the successful experimental verification of the suitable concentration range. The problem of the mathematical modelling of non-ideal, non-linear equilibrium chromatography using eqn. 1 was

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described thoroughly by Smit *et al.*[7,8]. The algorithm of the numerical procedure is based on an explicit method for the solution of partial differential equations.

The numerical solution of eqn. 1 for the boundary conditions corresponding to the scale-up of liquid chromatography was given by Cowan *et al.*[9] for non-equilibrium chromatography. They applied a kinetic function describing a first-order reversible reaction.

Guiochon and co-workers[10–15] applied a non-traditional approach to the solution of eqn. 1. They used the observation that the solution of eqn. 1 is similar to the numerical solution of a simpler equation for an ideal model, provided that the increments of space and time are suitably chosen (not too small).

The aim of this work was to construct a computer program for the numerical solution of eqn. 1 for an arbitrary case of the equilibrium isotherm and for an arbitrary volume and concentration of sample injected that should also be applicable for a two-component system.

THEORY

Development of the model

The model is based on the well known differential equation describing the mass balance of the component examined on the column at a point x and time t:

$$\frac{\partial C(x, t)}{\partial t} + \frac{1 - \varepsilon}{\varepsilon} \cdot \frac{\partial \bar{C}(x, t)}{\partial t} = D \cdot \frac{\partial^2 C(x, t)}{\partial x^2} - u \cdot \frac{\partial C(x, t)}{\partial x} \quad (1)$$

where u is the linear velocity of the mobile phase (cm/s), D the axial dispersion coefficient (cm^2/s), ε the void fraction of the bed, $\bar{C}$ the concentration of the examined component in the stationary phase (mol/l of the stationary phase) and C the concentration of the examined component in the mobile phase (mol/l).

The velocity is assumed to be constant within the whole column cross-section S ($u = Q/S\varepsilon$), where Q is the flow-rate (cm^3/s). The coefficient D is also assumed to be constant for the given experimental conditions, *i.e.*, for a given temperature, viscosity, density and velocity of the mobile phase, sorbent particle size, examined component, column diameter, etc. To determine its value, a chromatographic experiment under the conditions when the component examined is not retained must be performed and evaluated, *e.g.*, by using the analytical solution[4]. As far as the change in mass with time on the sorbent, $\partial\bar{C}/\partial t$, is concerned, it can be assumed that the whole process is at equilibrium and that the functional dependence between C and $\bar{C}$ [$\bar{C} = \bar{C}(C)$, the equilibrium isotherm] exists. The experimental procedures that enable this dependence to be found have already been described[16,17]. It is obvious that all the parameters characterizing the column, the mobile phase, the examined component and the experimental conditions necessary for the solution of eqn. 1, *i.e.*, for the determination of the course of the function $C(x, t)$, are easily accessible experimentally.

Numerical solution

Replacing the term $\partial\bar{C}/\partial t$ by the term $(\partial\bar{C}/\partial C)(\partial C/\partial t)$ and introducing the dimensionless variables $\tilde{x} = x/L$ and $\tilde{t} = t/t_0$, where L is the column length and $t_0 = L/u$, eqn. 1 can be written as

$$\left(1 + \frac{1-\varepsilon}{\varepsilon} \cdot \frac{\partial \bar{C}}{\partial C}\right) \frac{\partial C(\tilde{x}, \tilde{t})}{\partial \tilde{t}} = \frac{1}{Pe} \cdot \frac{\partial^2 C(\tilde{x}, \tilde{t})}{\partial \tilde{x}^2} - \frac{\partial C(\tilde{x}, \tilde{t})}{\partial \tilde{x}} \tag{2}$$

where $Pe = uL/D$ is the Pecklet number. The boundary conditions are given by the equations

$$\begin{aligned} P &= C - \frac{1}{Pe} \cdot \frac{\partial C}{\partial \tilde{x}}; \qquad \tilde{x} = 0, \tilde{t} \geqslant 0 \\ \frac{\partial C}{\partial \tilde{x}} &= 0; \qquad \tilde{x} = 1, \tilde{t} \geqslant 0 \end{aligned} \tag{3}$$

where P is the substance concentration in the input mobile phase. The following initial condition is assumed:

$$C(\tilde{x}, 0) = 0; \qquad \tilde{x} \in \langle 0, 1 \rangle \tag{4}$$

To solve eqn. 2, we use the Cranck–Nicolson implicit method[18]. The interval defined by the chromatographic peak is divided into n parts and the substitution of the derivations in eqn. 2 is performed in the usual way. For the expression in parentheses on the left hand side of eqn. 2 we introduce the symbol F; it is obvious that F is a function of C. This term can be replaced, in the agreement with the Cranck–Nicolson method, by the average:

$$F_i^{j+1/2,(m+1)} \approx \frac{1}{2} [F_i^{j+1,(m+1)} + F_i^j] \tag{5}$$

where j is related to the time level, i to the spatial coordinate and m is the iterative step of the solution of eqn. 2; for $m = 0$ we choose $F_i^{j+1,(0)} = F_i^j$.

Eqn. 1 or 2 can also be applied for the description of a chromatographic process for a two-component mixture with components 1 and 2. If the equilibrium isotherms expressed generally as $\bar{C}_k = \bar{C}_k(C_1, C_2)$, where $k = 1$ or 2, are assumed, then instead of eqn. 2 we have a system of two partial differential equations:

$$\left(1 + \frac{1-\varepsilon}{\varepsilon} \cdot \frac{\partial \bar{C}_k}{\partial C_k}\right) \frac{\partial C_k}{\partial \tilde{t}} + \frac{1-\varepsilon}{\varepsilon} \cdot \frac{\partial \bar{C}_k}{\partial C_l} \cdot \frac{\partial C_l}{\partial t} = \frac{1}{Pe_k} \cdot \frac{\partial^2 C_k}{\partial \tilde{x}^2} - \frac{\partial C_k}{\partial \tilde{x}} \tag{6}$$

$$k, l = 1, 2, k \neq l$$

The value of the derivation $\partial \bar{C}_k / \partial C_k$ or $\partial \bar{C}_k / \partial C_l$ can be approximated by an equation analogous to eqn. 5. For the derivations in eqn. 6 we use the following substitutions:

$$\frac{\partial C_k}{\partial \tilde{t}} \approx \frac{C_{k,i}^{j+1,(m+1)} - C_{k,i}^j}{\Delta \tilde{t}} \tag{7}$$

$$\frac{\partial C_k}{\partial \tilde{x}} \approx \frac{1}{2}\left[\frac{C_{k,i+1}^{j+1,(m+1)} - C_{k,i-1}^{j+1,(m+1)}}{2\Delta\tilde{x}} + \frac{C_{k,i+1}^{j} - C_{k,i-1}^{j}}{2\Delta\tilde{x}}\right] \tag{8}$$

$$\frac{\partial^2 C_k}{\partial \tilde{x}^2} \approx \frac{1}{2}\left[\frac{C_{k,i+1}^{j+1,(m+1)} - 2C_{k,i}^{j+1,(m+1)} + C_{k,i-1}^{j+1,(m+1)}}{2\Delta\tilde{x}^2} + \frac{C_{k,i+1}^{j} - 2C_{k,i}^{j} + C_{k,i-1}^{j}}{2\Delta\tilde{x}^2}\right] \tag{9}$$

for $m = 0$ we choose $C_{k,i}^{j+1,(0)} = C_{k,i}^{j}$.

After the substitution of these approximations into eqn. 6, we obtain (in agreement with the Cranck–Nicolson method) a system of linear equations for unknown $C_{k,i}^{j+1}$ ($k = 1, 2; i = 1, 2, \ldots n + 1$). It is evident that the matrix of this system is tridiagonal.

The concept of the program is as follows. A number of iteration steps are tested on the basis of comparison of an integral value corresponding to the amount of substances contained in the chromatographic peaks with the amount of substances injected on to the column. The difference in these two values must be less than 0.1%. After the computation of a concentration profile for each time level, the initial and end points of the peak are determined as a concentration C greater than or equal to one thousandth of the maximum concentration in the peak. The magnitude of a differential step in the coordinate ($\Delta\tilde{x}$) is adjusted so that the maximum number of points in the peak is 500. The differential step in time ($\Delta\tilde{t}$) is chosen first to be 0.0001 and after the peak end has passed the beginning of the column $\Delta\tilde{t} = 0.001$.

In the computation, the following equations were used to describe the isotherms:

one-component system:

$$\bar{C} = \frac{AC}{1 + BC} \tag{10}$$

two-component system:

$$\bar{C}_k = \frac{A_k C_k}{1 + B_1 C_1 + B_2 C_2}, \qquad k = 1, 2 \tag{11}$$

where A and B are constants.

A rectangular shape was assumed for the input signal, *i.e.*, P in eqn. 3 takes the value C_0 (the concentration of a component determined in an injected sample), and for the time greater then the time necessary for the passing of the injected volume, the value 0.

The input data for the program are as follows: the column length L, its diameter *I.D.*, the void fraction of the bed ε, the mobile phase flow-rate Q, the volume injected V_D, the concentration in the injected sample C_{0k}, the axial dispersion coefficients D_k and the equilibrium isotherm parameters A_k and B_k. The program output represents the time course of the concentration at the end of the column, C_k (L, t), or at an arbitrary point, as the case may be. The parameters used for the characterization of the chromatographic peaks, *i.e.*, the statistical moments (from the first to the fourth reduced statistical moment), the capacity factor, the plate number, etc., can be determined from this concentration course.

All the computations were performed using a PDP 11/23 microcomputer with a 128K memory under the RSX 11 M system. The programs were written in Fortran F 77. The computation of the chromatogram for one component took 2–3 h and for a two-component system 8–12 h.

RESULTS AND DISCUSSION

The accuracy of the program for a one-component system was verified for a linear isotherm by comparison with the analytical expression for the statistical moments. For $L = 25$ cm, $I.D. = 0.8$ cm, $\varepsilon = 0.375$, $Q = 0.6$ ml/min, $V_D = 0.1$ ml, $D = 0.0008$ cm^2/s, $A = 1.5$ and $B = 0.0$, the difference was 0.17% for the first, 2.5% for the second and 4.2% for the third moments. These differences are regarded as negligible. For a non-linear isotherm, the analytical expression reported by Jaulmes *et al.*[6] was used for the comparison. The course of the isotherm described both by eqn. 10 and by the second-order polynomial (the expression for which the analytical relationship was derived) is illustrated in Fig. 1a. Fig. 1b, c and d show that the difference in the courses of the peaks obtained by the two methods of computation increases with increasing load of the column, *i.e.*, in a region of concentrations such that the corresponding isotherms differ. When in the numerical computation the same polynomial was used for the description of the equilibrium dependence $\bar{C} \sim C$, the courses of the peaks were identical even for greater loadings of the column.

For a linear isotherm, the well known relationships between the separation coefficient K_D (see eqn. 10) ($K_D = A$ for $B = 0$) and the capacity factor k' [$k' = K_D(1 - \varepsilon)/\varepsilon$] and the linearity between the number of plates N and the column length L were verified. In instances the result was in good agreement with theory[1]. The influence of the coefficient D on the width and asymmetry of a chromatographic peak is evident from Fig. 2a. The influence of the separation coefficient K_D on the peak width is shown in Fig. 2b and demonstrates the course of the amount of substance on the column at various times. The time points are chosen so that the leading edges of the peaks cover the same distances. Fig. 2b shows that a peak moving more slowly (with a highher K_D value) is narrower inside the column. The reality that at the column outlet it is broader is due to the fact that it flows out more slowly from the column.

The influence of a non-linear course of the equilibrium isotherm on the peak asymmetry and on the position, *i.e.*, on the capacity factor, is evident from Fig. 3. Although the non-linearity of the isotherm is not very pronounced ($B = \pm 0.2$), the courses of both peaks (Fig. 3b and c) differ cosiderably from that for a linear isotherm (Fig. 3a).

The program constructed for one component was used for the evaluation of the influence of the real apparatus function of the detector (a flow-through radioactivity detector designed in our laboratory) (see Fig. 4a) on the peak leaving the column. Fig. 4b and c compare the peaks before and after the convolution with the detector apparatus function. It is evident that for a 250 × 8 mm I.D. column an injection volume of 100 μl, the influence of the detector is negligible.

On the basis of the results obtained, we conclude that the program for the numerical solution of eqn. 1 for one component is correct and can be used for experimental verification.

This program constructed for one component formed the basis of the

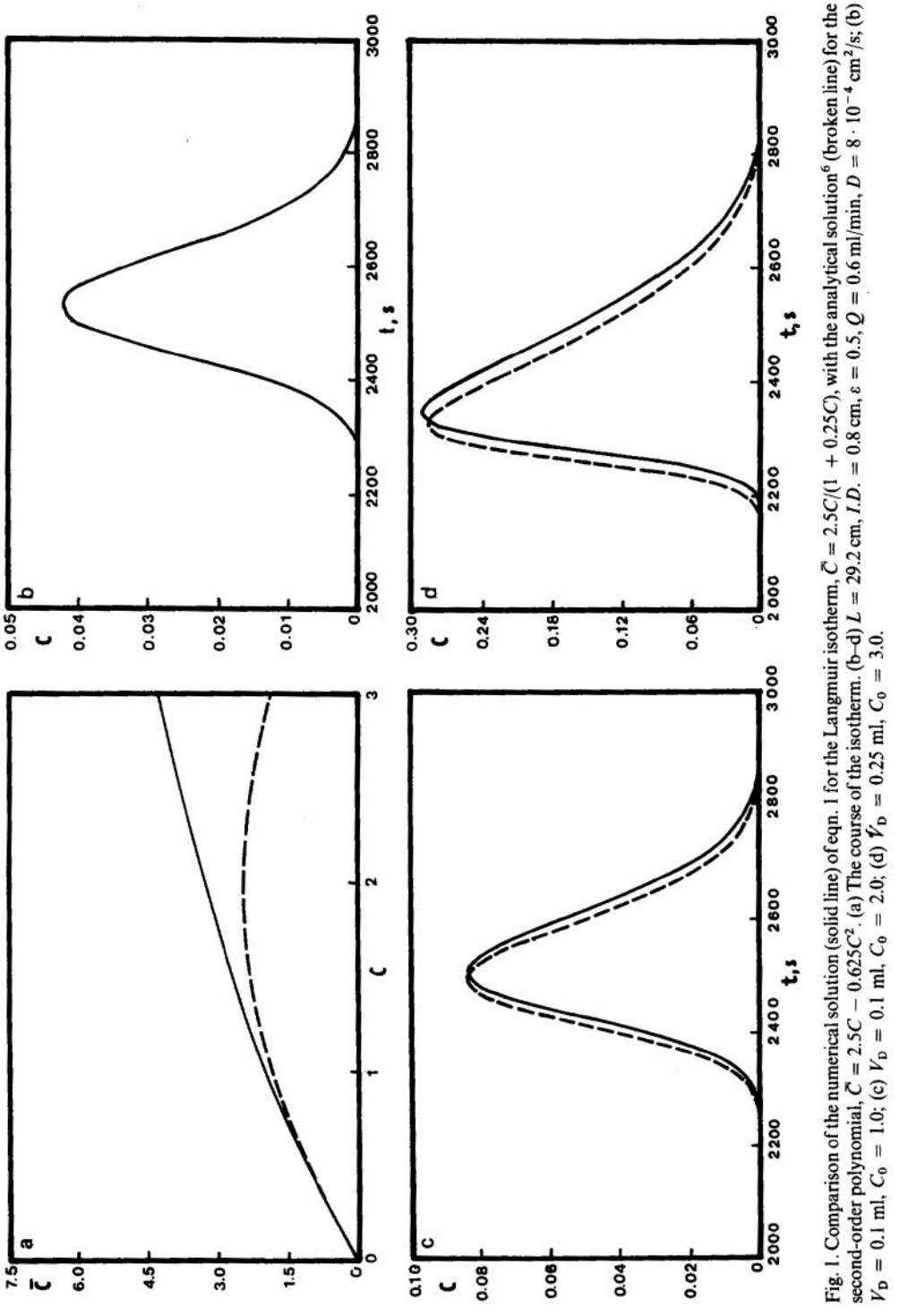

Fig. 1. Comparison of the numerical solution (solid line) of eqn. 1 for the Langmuir isotherm, $\bar{C} = 2.5C/(1 + 0.25C)$, with the analytical solution[6] (broken line) for the second-order polynomial, $\bar{C} = 2.5C - 0.625C^2$. (a) The course of the isotherm. (b–d) $L = 29.2$ cm, $I.D. = 0.8$ cm, $\varepsilon = 0.5$, $Q = 0.6$ ml/min, $D = 8 \cdot 10^{-4}$ cm^2/s; (b) $V_D = 0.1$ ml, $C_0 = 1.0$; (c) $V_D = 0.1$ ml, $C_0 = 2.0$; (d) $V_D = 0.25$ ml, $C_0 = 3.0$.

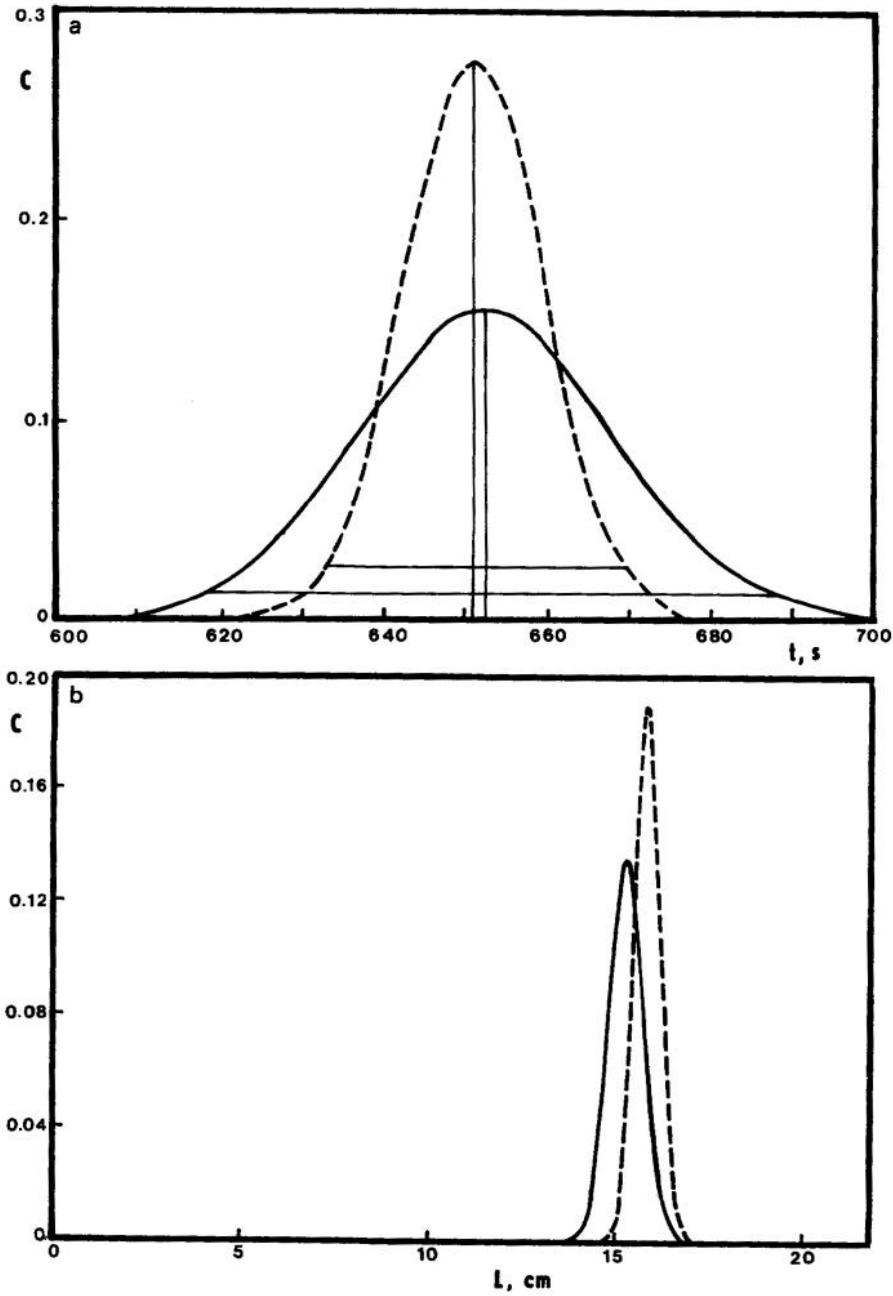

Fig. 2. Computations for linear chromatography: $L = 25$ cm, $I.D. = 0.4$ cm, $\varepsilon = 0.375$, $Q = 0.2$ ml/min, $V_D = 0.02$ ml, $C_0 = 1.0$. (a) Influence of the axial dispersion coefficient: $D = 1.5 \cdot 10^{-4}$ cm^2/s (broken line), $D = 5 \cdot 10^{-4}$ cm^2/s (solid line), $K_D = 0.5$. (b) Influence of the separation coefficient: $K_D = 0.5$ (solid line), $K_D = 2.0$ (broken line), $D = 5 \cdot 10^{-4}$ cm^2/s.

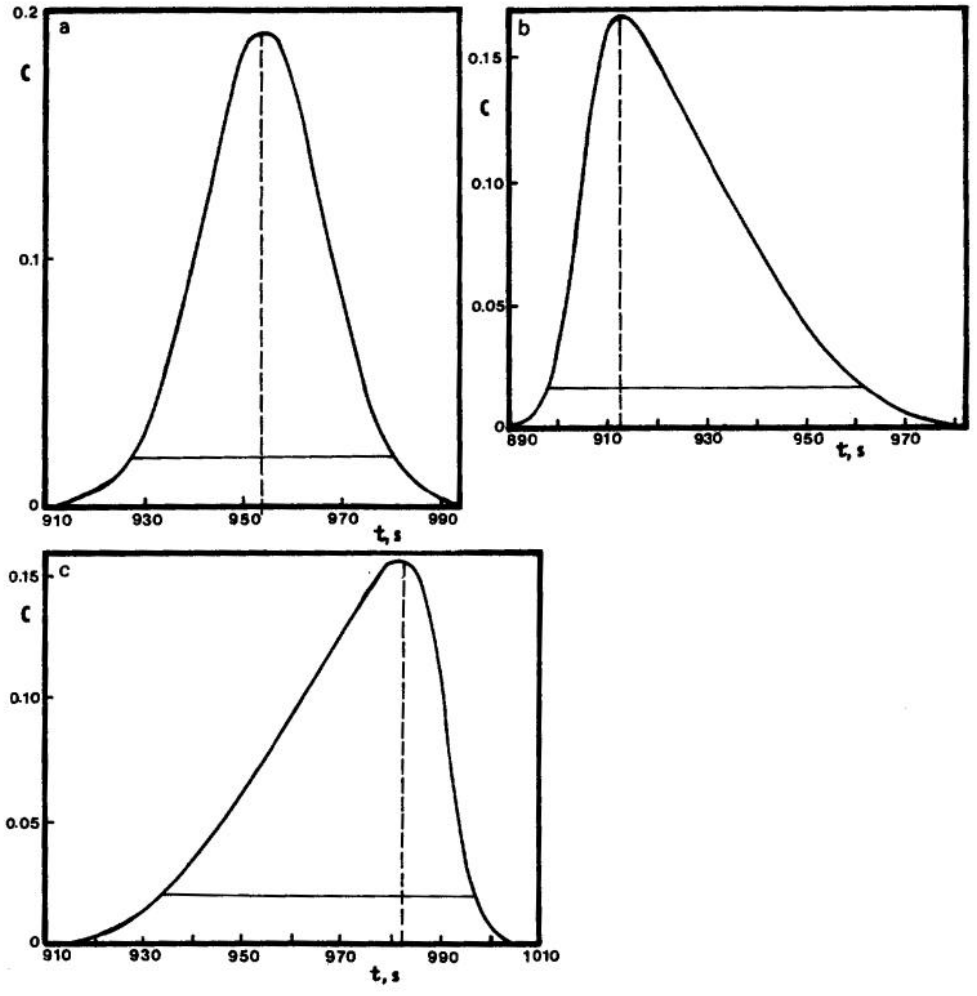

Fig. 3. Influence of the shape of the isotherm on the shape of the peak for the following conditions: $L = 25$ cm, $I.D. = 0.4$ cm, $\varepsilon = 0.375$, $Q = 0.2$ ml/min, $V_D = 0.02$ ml, $C_0 = 1.0$, $D = 1.5 \cdot 10^{-4}$ cm^2/s. (a) $A = 1.0$, $B = 0.0$; (b) $A = 1.0$, $B = 0.2$; (c) $A = 1.0$, $B = -0.2$.

construction of a program for two components. As an equilibrium function we used eqn. 11, which represents the Langmuir isotherm[19,20] for positive values of the coefficients B. For negative coefficients B, only the range of concentrations when the denominator of eqn. 11 is positive has a physical sense.

The aim of the numerical experiments was to verify the accuracy of the program on the basis of the influence of column overloading on the shape and resolution of peaks for various equilibrium isotherms given by eqn. 11, *i.e.*, for various values of B under the same conditions (see Figs. 5, 6 and 7).

With negative values of B and considering the limited definition range, overloading may be realized by increasing the volume injected and not the concentration. Therefore, the results of both methods of overloading were compared

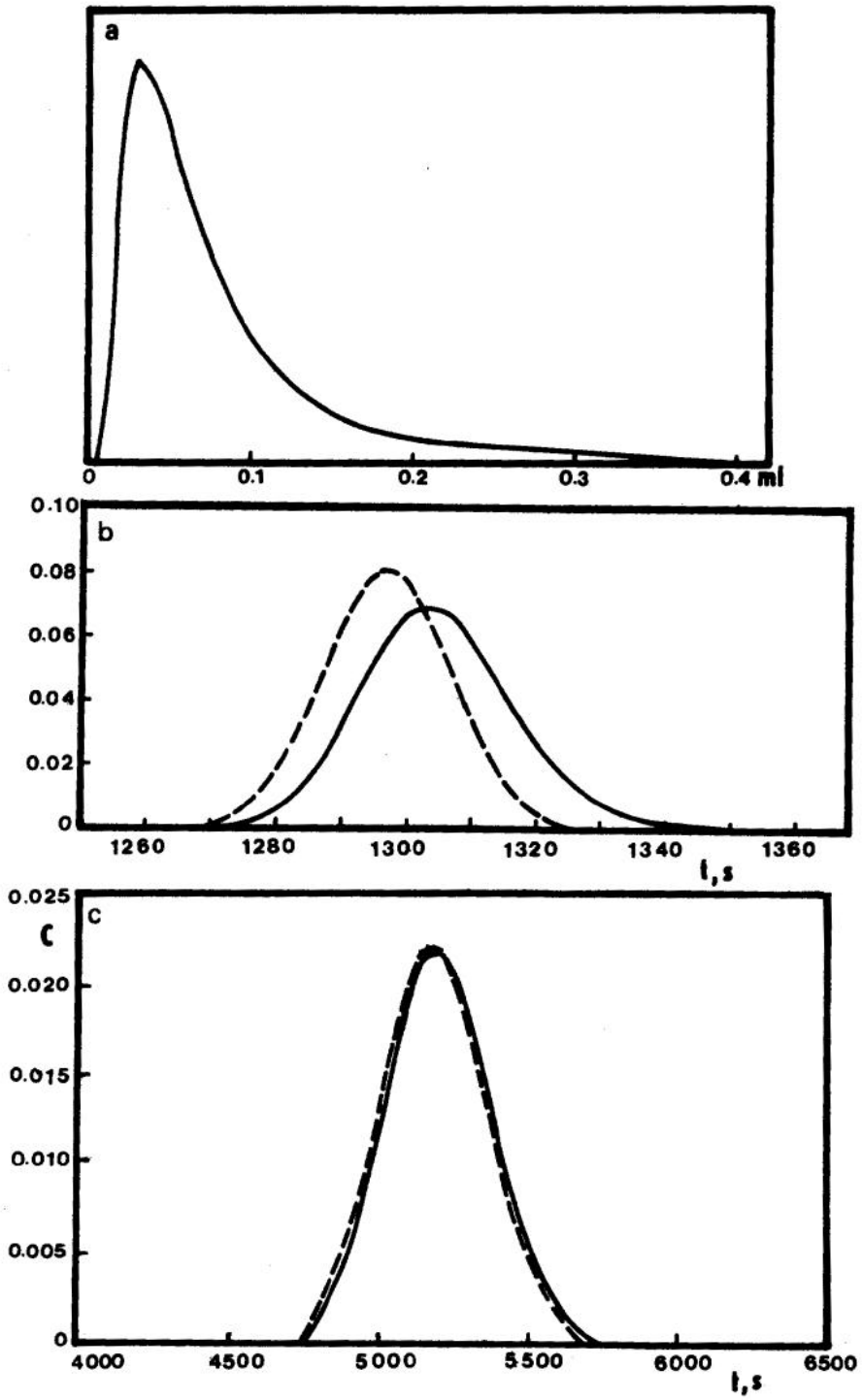

Fig. 4. Comparison of the chromatographic peak before convolution (broken line) and after convolution (solid line) with the apparatus function of a flow-through radioactivity detector. Conditions used: $L = 25$ cm, $\varepsilon = 0.375$, $Q = 0.6$ ml/min, $C_0 = 1.0$, $A = 6.0$, $B = 0.0$. (a) Shape of the apparatus function; (b) *I.D.* = 0.4 cm, $V_D = 0.02$ ml, $D = 1.5 \cdot 10^{-4}$ cm^2/s; (c) *I.D.* = 0.8 cm, $V_D = 0.1$ ml, $D = 8 \cdot 10^{-4}$ cm^2/s.

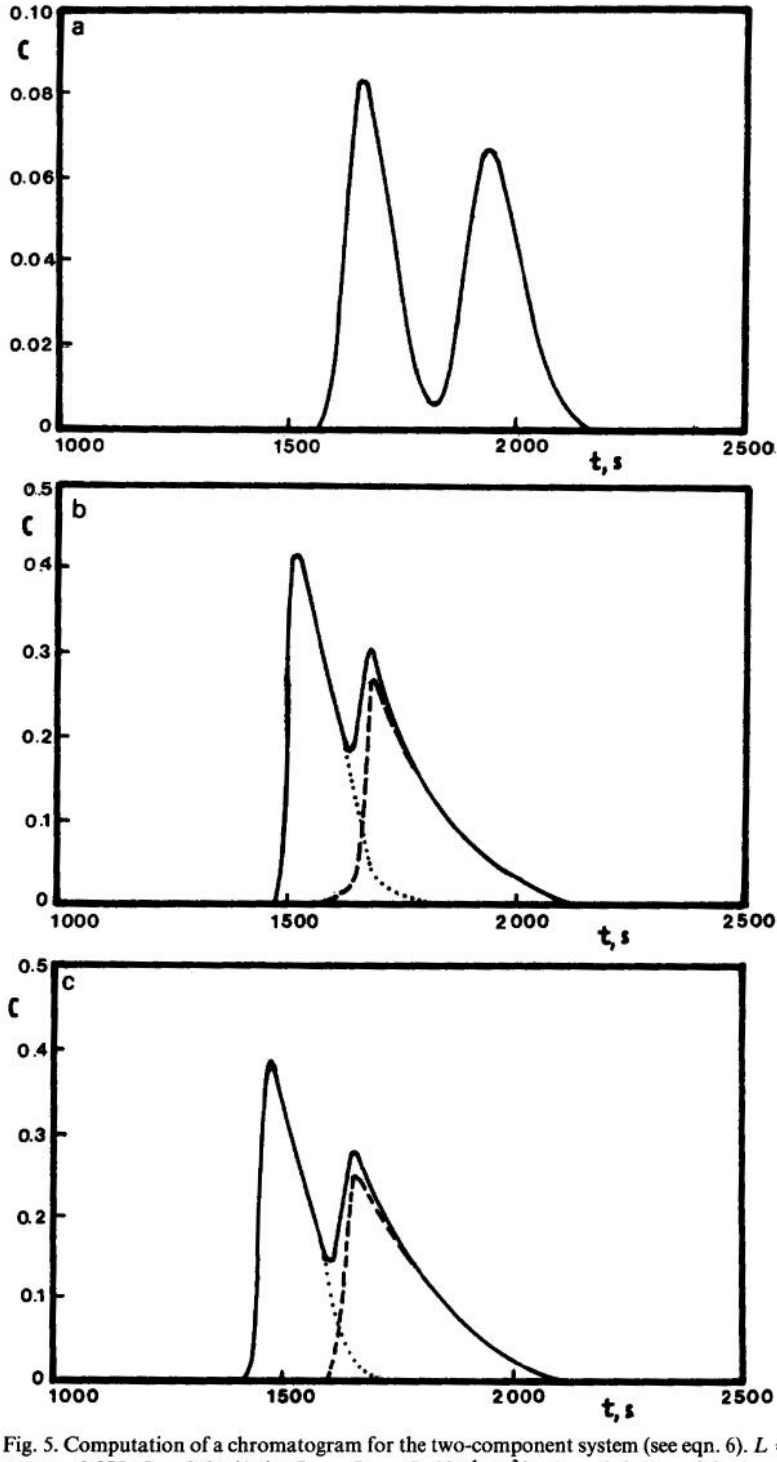

Fig. 5. Computation of a chromatogram for the two-component system (see eqn. 6). $L = 25$ cm, $I.D. = 0.8$ cm, $\varepsilon = 0.375$, $Q = 0.6$ ml/min, $D_1 = D_2 = 5 \cdot 10^{-4}$ cm^2/s, $A_1 = 1.6$, $B_1 = 0.3$, $A_2 = 1.96$, $B_2 = 0.3$. (a) $V_D = 0.1$ ml, $C_{01} = C_{02} = 1.0$; (b) $V_D = 0.5$ ml, $C_{01} = C_{02} = 1.0$; (c) $V_D = 0.1$ ml, $C_{01} = C_{02} = 5.0$. The individual components are marked by the broken line.

first for the case when the definition range of eqn. 11 was unlimited (both coefficients B were positive). As follows from Fig. 5b and c, the difference is not pronounced; for the higher concentrations the retention times are slightly lower and the resolution higher.

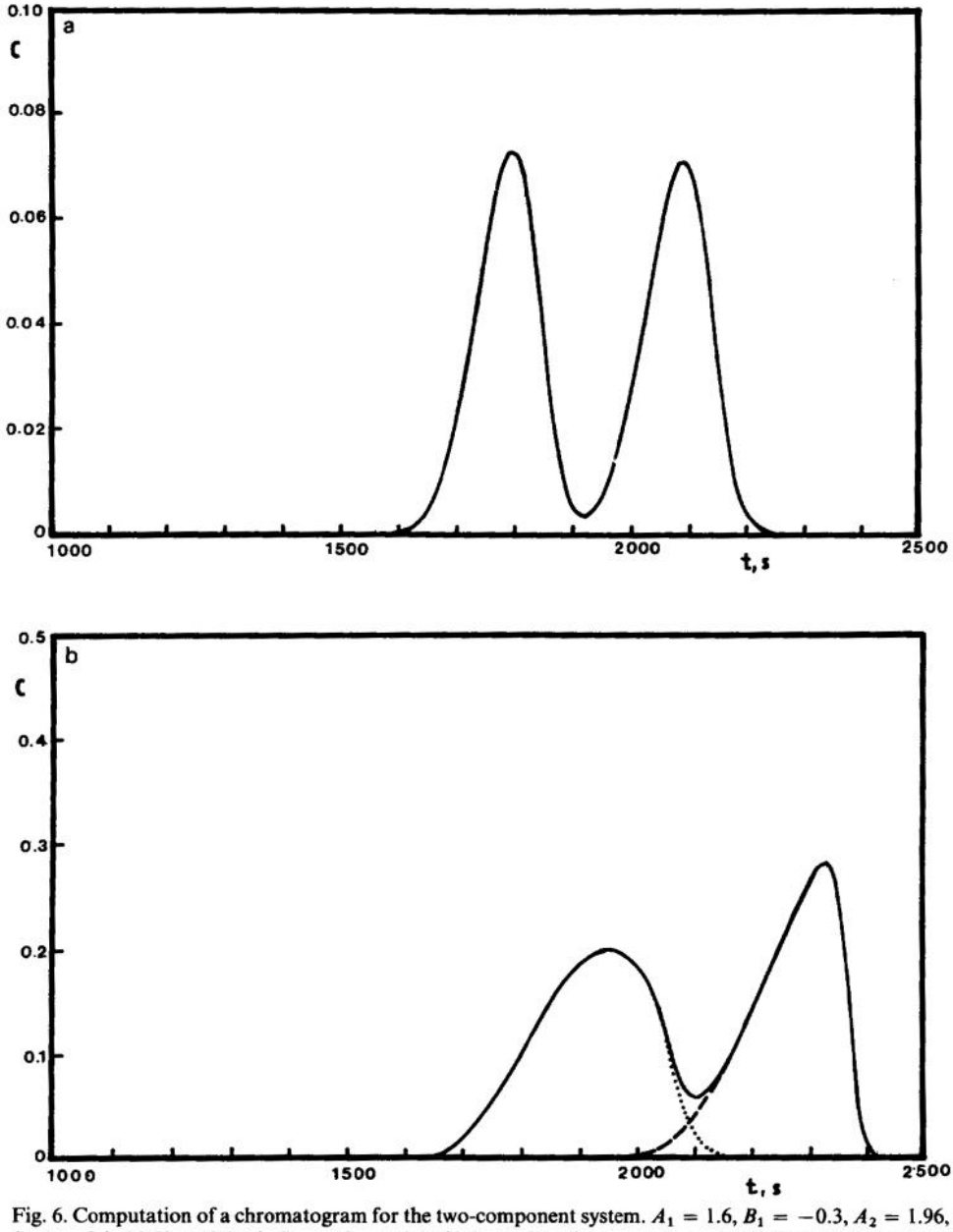

Fig. 6. Computation of a chromatogram for the two-component system. $A_1 = 1.6$, $B_1 = -0.3$, $A_2 = 1.96$, $B_2 = -0.3$. (a) $V_D = 0.1$ ml, $C_{01} = C_{02} = 1.0$; (b) $V_D = 5.0$ ml, $C_{01} = C_{02} = 1.0$. Other conditions as in Fig. 5.

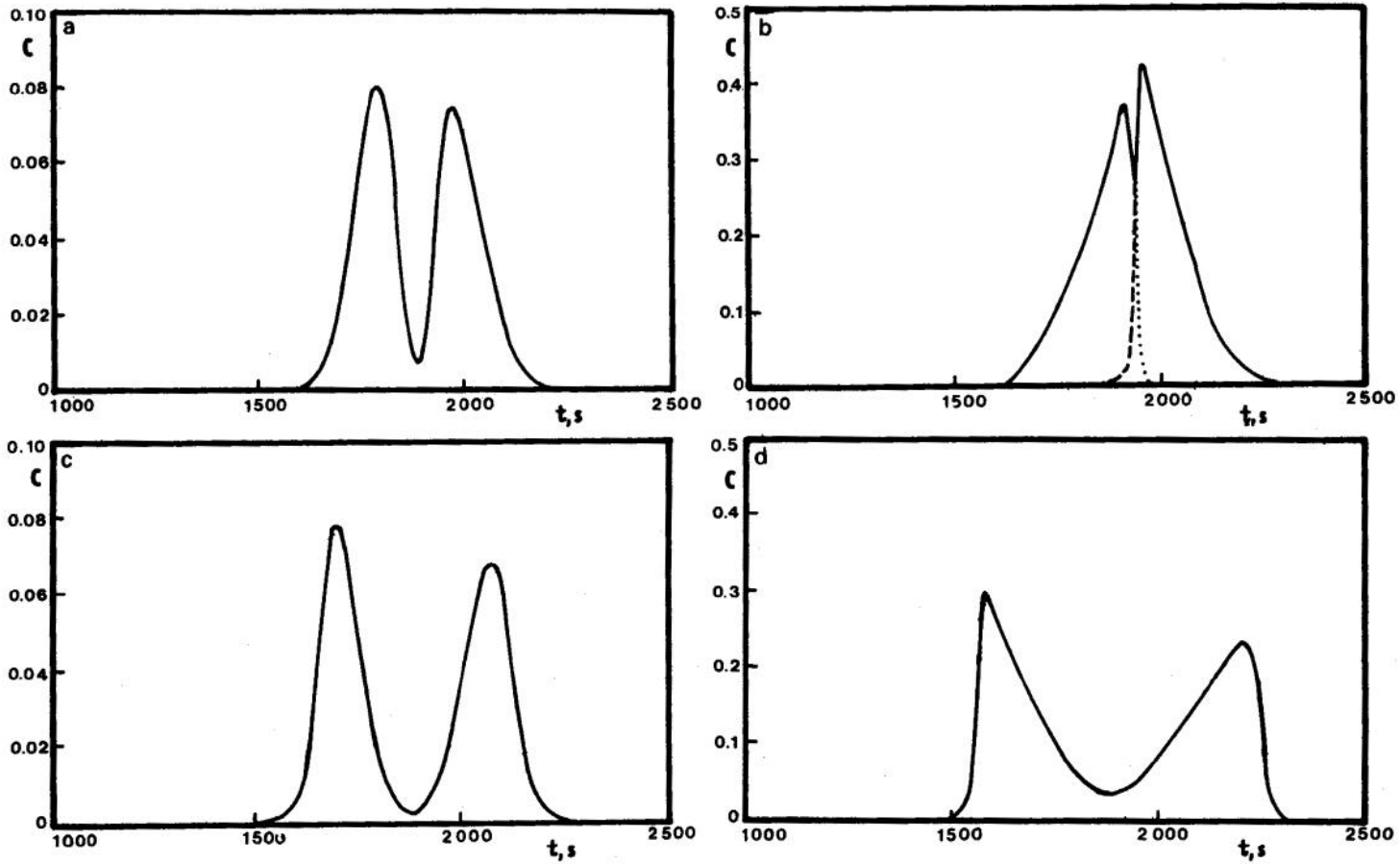

Fig. 7. Computation of a chromatogram for the two-component system. (a) $A_1 = 1.6$, $B_1 = -0.3$, $A_2 = 1.96$, $B_2 = 0.3$, $V_D = 0.1$ ml, $C_{01} = C_{02} = 1.0$; (b) A_1, B_1, A_2 and B_2 as in (a), $V_D = 0.5$ ml, $C_{01} = C_{02} = 1.0$; (c) $A_1 = 1.6$, $B_1 = 0.3$, $A_2 = 1.96$, $B_2 = -0.3$, $V_D = 0.1$ ml, $C_{01} = C_{02} = 1.0$; (d) A_1, B_1, A_2 and B_2 as in (c), $V_D = 0.5$ ml, $C_{01} = C_{02} = 1.0$. Other parameters as in Fig. 5.

The chromatograms in Figs. 5–7 demonstrate that in all instances, when the amount injected is increased, the retention times t_R are shifted to lower or higher values depending on whether B is positive or negative. From the standpoint of the resolution, the most disadvantageous case is when $B_1 < 0$ and $B_2 > 0$. To judge the effect of the mutual influence of the first and second components, let us compare the retention times of one component (for a given value of B) with the retention times of the same component but for another value of B of the second component. For example, the retention times of the first component t_{R1} on the chromatograms in Fig. 7a and b are lower than t_{R1} in Fig. 6a and b, but t_{R2} on the same chromatograms (Fig. 7a and b) are higher than t_{R2} in Fig. 5a and b. Similarly, we can compare Fig. 7c and d with Fig. 5a and b for the first component and with Fig. 6a and b for the second component. All these comparisons show the influence of the second component (or its corresponding B value) on the retention time of the competitive component.

The program may be used for a real system on the condition that the real values ε, D_k, $\bar{C}_k = \bar{C}_k(C_1, C_2)$ and possibly the shape of the input signal have been determined.

CONCLUSION

The various methods for modelling of the chromatographic process can be found in the literature[21–24]. We decided to solve eqn. 1 using the procedure that, according to Guiochon and Katti's review dealing on preparative chromatography[25], belongs to the group of solutions that are available for the quasi-ideal problem, *i.e.*, the kinetics of mass transfer must be rapid and independent of the concentration, and must be accounted for by an apparent diffusion coefficient. The advantage of this approach consists in its applicability to multi-component systems, whereas the approach based on the real kinetic function of mass transfer and a non-linear isotherm is not applicable to the study of the separation between two compounds.

In subsequent work we shall examine the experimental verification of the numerical solution discussed above. In addition, we shall compare the results with those obtained following an approach similar to the work of Ghodbane and Guiochon[13] and with the data obtained in different ways (mixed cells model) developed in our laboratory[24].

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