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THEORETICAL ANALYSIS OF NON-LINEAR PREPARATIVE LIQUID CHROMATOGRAPHY

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SUMMARY

The migration of a high-concentration, multi-component band in chromatography is a particular case of the reaction–diffusion processes. The various approaches to the solution of the system of partial differential equations obtained are reviewed for the cases of a pure compound and of a binary mixture. Particular emphasis is placed on the derivation of accurate, meaningful results while minimizing the amount of experimental work required for the determination of the parameters needed for the prediction of the band profiles. From this point of view, the simple wave theorem is important, as it offers an attractive approach for the determination of competitive equilibrium isotherms.

INTRODUCTION

This paper reviews the results of an investigation of the fundamentals of chromatography at high concentration, when large sample pulses are injected in a mobile phase of constant or slowly changing composition (isocratic or gradient elution modes) or in a mobile phase containing additives which are about as strongly retained as the components of the sample (system peaks), when these pulses are injected in front of a wide plug of a solution of a strongly retained compound (displacement) or when a step of a concentrated solution is rapidly introduced into the column (frontal analysis). Although most of the results discussed here apply to all retention mechanisms used in chromatography, most of the examples are taken from adsorption chromatography. Some applications, however, may require a modified approach, such as some forms of ion chromatography, for which a charge balance equation is needed to maintain electrical neutrality of the elementary column slice. Finally, although our investigation is mainly relevant to the modern, high-performance implementations of chromatography, it also applies to situations where the kinetics of mass transfers between phases or the kinetics of the retention mechanisms are slow, as we consider near-equilibrium models only as a special case of the kinetic

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models which can account for all experimental conditions under which chromatography takes place.

Analytical chromatography

The classical theoretical investigations of chromatography have been carried out essentially for the purpose of understanding the behavior of columns used for analytical applications¹. They have been developed within the framework of the signal theory. The results of these studies permit the prediction of the moments of a compound band, and hence its position (retention data), its noise (here, the band width), its asymmetry, the ratio of the band position to its noise (in chromatographic terms the column efficiency) and the resolution between two closely eluted bands (the Rayleigh coefficient). They describe the influence of the experimental conditions on these various parameters, permit the optimization of the column resolution or of the analysis time and the use of the chromatographic data for qualitative and quantitative analysis. These predictions are made from independent physico-chemical data regarding the thermodynamics and kinetics of the equilibrium involved in the chromatographic process (Henry equilibrium constant, molecular diffusion coefficient, rate constants, etc.)^{1,2}. Fundamentally, the classical theory of chromatography provides the same information and satisfies the same needs as the similar theories of spectroscopic methods.

Experimentally, it is observed that, under classical analytical conditions (small sample amount), the chromatographic signal is nearly symmetrical and its position and width are essentially independent of the sample size. In agreement with theory, the characteristics of the band can be expressed by and summarized in the first few moments¹⁻⁴, *i.e.*, the zeroth moment, which characterizes the amount of material injected, the first moment, which is a definition of the retention time, and the second centered moment, related to the column efficiency (through the height equivalent to a theoretical plate). In practice, these first three moments are sufficient to characterize the profile of elution bands in analytical chromatography. Deviations from a symmetrical profile can be measured by the third (asymmetry) and fourth (excess) centered moments^{3,4}. As the main purpose is analytical and since extremely sensitive detectors are available, minute amounts of samples are injected, the chromatographic process is linear and the characteristics of the bands of the different components of a mixture are independent of each other and of the sample size. This makes qualitative analysis by chromatography a viable proposition.

Mathematically, such phenomena can be modeled using linear differential equations, obtained by writing the mass balance of each component of the sample in a column slice^{1,5}. Multi-component problems are easy to solve, because they are uncoupled. The superposition principle holds and the resolution analysis can be directly derived from the similar analysis of the behavior of single-component processes. This makes the optimization of the analysis time for the complete separation of a mixture a fairly simple investigation. The proper model is represented by the set of linear partial differential equations for each single compound and the method to solve this model is the Laplace transform followed by moment analysis.

Preparative (non-linear) chromatography

The purpose of preparative chromatography is different from that of analysis^{6,7}.

Signal information is less important than the preparation of purified products. Although signal information parameters characterizing retention and the separation between bands are still valuable information for the separation scientist, during the development of a new method, the critical factor is the production rate at a certain purity.

Experimentally, samples with a very large amount and volume have to be considered. The amount of material injected into a column with respect to unit cross-sectional area exceeds by one or several orders of magnitude that conventionally used with analytical columns. The injection of these amounts cannot be done instantaneously. In a number of instances, for solubility reasons, the sample must be diluted in a volume of mobile phase or solvent which is large with respect to the elution band volume of a non-retained compound. It is rare, however, that the process can be considered as linear.

Theoretically, as the concentrations of the bands in the column are high and the volumes injected are large, the multi-component problem cannot be tackled as in analytical chromatography. The mass balance equation for a single component is a non-linear partial differential equation for which there is no general analytical solution^{5,8}. An analytical solution is possible only in some special cases, or with some simplifying assumptions which are valid only in particular cases (very small degree of overload, column of infinite efficiency, etc.)^{1,5,9,10}. Further, in the case of a multi-component sample, the principle of superposition no longer applies. The system of non-linear partial differential equations which corresponds to such problems is coupled, because the equilibrium isotherms or the retention kinetics of each component depend on the concentration of *all* the components of the system¹¹. This makes the solution of a multi-component problem all the more difficult to obtain.

Overview of the history of non-linear chromatographic theory

The theory of non-linear chromatography has developed slowly over the years. Wilson⁵ was the first to discuss the mass balance equation for a single compound and understood the difficulties arising from the existence of a velocity associated with each concentration and of the concentration dependence of this velocity. De Vault¹² recognized the possibility of the formation and propagation of concentration discontinuities in the ideal model. Weiss¹³, Walter¹⁴ and Glueckauf¹¹ published important papers discussing the solution of the system of mass balance equations of chromatography for a pure compound, using the ideal model (*i.e.*, assuming an infinitely efficient column). Thomas¹⁵ and Goldstein¹⁶ gave an analytical solution for the band profile of a pure compound, using a kinetic model, with Langmuir kinetics of adsorption-desorption. This solution was recently used successfully by Wade *et al.*¹⁷ to account for band profiles obtained in affinity chromatography. Rhee *et al.*¹⁸ and Guiochon and Jacob¹⁹ developed the application of the characteristic theory to the solution of the ideal model and calculated elution profiles and breakthrough curves using computer programs. Houghton²⁰ and Yeroshenkova *et al.*²¹ derived an approximate analytical solution valid at low concentrations, when the band broadening effect of the non-linear behavior of the isotherm is still small compared with the contributions of the axial dispersion and the kinetics of radial mass transfers. Recently, numerical solutions easy to implement have been described, which permit the calculation of the elution profile of large samples of pure compounds, knowing their

equilibrium isotherm and the column efficiency⁸. The experimental results are in excellent agreement with the results of these theoretical calculations^{22,23}. An analytical solution has been derived in the case of a Langmuir isotherm⁹.

The multi-component problem was investigated very early, but progress has been very slow. Glueckauf²⁴ gave an incomplete analytical solution of the ideal model for a binary mixture with a Langmuir competitive isotherm. Aris and Amundson²⁵ and Rhee and co-workers²⁶⁻³⁰ published an excellent discussion of the Riemann problem (*i.e.*, frontal analysis) in this case. A discussion of the pulse problems has been reported recently³¹. Helfferich and Klein³² derived, within the framework of the ideal model, distance-time diagrams which may be used to describe the migration and progressive separation of a multi-component band. Their method, based on the use of the *h*-transform, is difficult and has never been extended to the case of real columns with a finite efficiency. The first numerical solution was described by Guiochon and Jacob¹⁹, but it was not entirely satisfactory (because of truncation errors the procedure was not mass conservative³³) and a systematic investigation of the effects of the competition between the components of a mixture was made only recently³⁴. The optimization of the experimental conditions for the preparation of one of the components of a binary mixture has been discussed by Knox and Pyper⁶, Cox and Snyder³⁵, Katti and Guiochon³⁶, Ghodbane and Guiochon³⁷ and Golshan-Shirazi and Guiochon^{38,39}.

After a slow beginning, the theory of non-linear chromatography has developed rapidly during the last few years, under the pressure resulting from the needs of the biotechnologies for powerful purification processes which can be applied to molecules very sensitive to degradation. These advances have been allowed by progress made in pure and applied mathematics.

The purpose of this work was the investigation of some new approaches to this theory and a discussion of their most salient results. We especially discuss the computer simulation of the migration and separation of chromatographic bands, the influence of the non-linear behavior of the isotherm, of the axial dispersion and of the coefficients of resistance to radial mass transfers and of the truncation errors. Finally, we present some new results, using the simple wave theory.

MATHEMATICAL MODEL OF NON-LINEAR LIQUID CHROMATOGRAPHY

The dynamic process which takes place in chromatography is the same as that which occurs in the flow bed reactor discussed in chemical engineering⁴⁰. It is a convection-diffusion mass transfer process, which is mass conservative. There is no chemical reaction in the chromatograph, so the mass of each compound involved is conserved. The process of adsorption-desorption or more generally the retention process can be considered, however, as a generalized reaction. Therefore, the chromatographic process is a particular case of reaction-diffusion processes⁴⁰⁻⁴². From a microscopic viewpoint, the process is stochastic. The molecules move at random along the column, according to a certain probability distribution. The mathematical model which applies is the Fokker-Planck equation⁴³, the solution of which is the probability distribution of the residence times of the molecules of the sample.

We discuss in this section the general properties of the relevant equations in the case of chromatography.

Reaction-diffusion equations

The reaction-diffusion equation can be written as follows, in the case of a multi-component problem:

$$\frac{\partial C_i^{v_j}}{\partial t} + \nabla \cdot (\vec{u}_0^{v_j} C_i^{v_j}) = \nabla \cdot (D_i^{v_j} \nabla C_i^{v_j}) + \varphi_i^{v_j}(C_1^{v_1}, C_2^{v_1}, \dots, C_1^{v_2}, C_2^{v_2}, \dots) \quad (1)$$

where $i = 1, 2, \dots$, represents the different components of the mixture studied, the coefficients v_1, v_2, \dots , represent the different phases contained in the system used, $C_i^{v_j}$ is the concentration of compound i in phase v_j , u_0 is the mobile phase velocity, D is the diffusion coefficient and φ is the reaction rate function.

In chromatography, it is convenient to distinguish three phases, instead of the conventional two phases. These three phases are the flowing mobile phase, $v_1 = m$, which occupies the volume between the packing particles, the stagnant mobile phase, $v_2 = p$, which is contained in the packing particle pores and exchanges freely with the flowing mobile phase (although in some cases, such as in size exclusion chromatography, it may have different physical properties), and the stationary phase, $v_3 = s$. Further, it is usually assumed that $u_i^s = D_i^s = 0$, that $u_i^p = 0$, that $u_i^m = u_0$, as the stagnant mobile phase does not move, and that $D_i^m = D$ is different from D_i^p , because of the difference in geometry and structure between the inter-particle and the extra-particle porosities.

In adsorption chromatography, the reaction involved in the retention mechanism is adsorption-desorption. Two possible models can be derived from eqn. 1, depending on whether we neglect or not the mass transfer processes in the pores of the column packing material.

Mass transfers proceed in the pores as fast as in the bulk. If the contribution of the mass transfer processes across pores to the equilibration kinetics is neglected, as a first approximation, we may write

$$\varphi_i^m = \varphi_i^m(C_1^m, C_2^m, \dots, C_1^s, C_2^s, \dots) \quad (2)$$

In almost all applications of chromatography, whether analytical or preparative, the kinetics is fast and the system is always close to equilibrium, although never at equilibrium except in one point at a given time. Accordingly, we may write the reaction rate function as

$$\varphi_i^m = F K_i [C_i^s - f_i(C_1^m, C_2^m, \dots)] \quad (3)$$

where K_i is the mass transfer coefficient for component i and F is the phase ratio. In liquid chromatography, we can neglect the sorption effect, since the molar volumes of the sample components are very nearly the same in both phases^{44,45}. Unlike in gas-liquid, gas-solid and liquid-liquid chromatography, in liquid-solid chromatography the boundary between the mobile and the stationary phases is fuzzy. The definitions of the volume occupied by the stationary phase and of the mobile phase hold-up time (t_0) and volume are unclear. Riedo and Kováts⁴⁶ gave a detailed discussion of this problem. They showed that the retention in liquid-solid adsorption chromatography can be described in terms of Gibbs excess free energies and

adsorption processes. It is not possible to define properly the surface concentration of the adsorbate without defining first a convention concerning the adsorption equilibrium^{45,46}. The most convenient convention in liquid chromatography is to assume that the mobile phase, if it is pure, or the weak solvent, if the mobile phase is a mixture or contains additive(s), is not adsorbed. The mass balance of the weak solvent is then an identity, but all adsorption isotherms must be reported with the same convention.

Hence, the flow velocity of the mobile phase may be considered as constant and, in the case of near-equilibrium chromatography, the reaction-diffusion equation system for a binary mixture becomes:

$$\frac{\partial C_1^m}{\partial t} + \vec{u}_0 \cdot \nabla C_1^m = D \nabla^2 C_1^m + FK_1 [C_1^s - f_1(C_1^m, C_2^m)] \quad (4)$$

$$\frac{\partial C_1^s}{\partial t} = -K_1 [C_1^s - f_1(C_1^m, C_2^m)] \quad (5)$$

$$\frac{\partial C_2^m}{\partial t} + \vec{u}_0 \cdot \nabla C_2^m = D \nabla^2 C_2^m + FK_2 [C_2^s - f_2(C_1^m, C_2^m)] \quad (6)$$

$$\frac{\partial C_2^s}{\partial t} = -K_2 [C_2^s - f_2(C_1^m, C_2^m)] \quad (7)$$

When $K_i \rightarrow \infty$, the process tends towards an equilibrium one. Then the concentration of each compound in the stationary phase is related to the mobile phase composition through the equation

$$C_i^s = q = f_i(C_1^m, C_2^m) \quad (8)$$

which is referred to as the equilibrium isotherm. In this case, $\partial C_i^s / \partial t = \partial f_i / \partial t$, and eqns. 4 and 6 become

$$\frac{\partial C_i^m}{\partial t} + F \frac{\partial f_i}{\partial t} + \vec{u}_0 \cdot \nabla C_i^m = D \nabla^2 C_i^m \quad i = 1, 2 \quad (9)$$

Mass transfers proceed at different rates in the pores and in the bulk. Here eqn. 1 should be written for the three phases that we must consider (flowing and stagnant mobile phases and stationary phase). We obtain

$$\frac{\partial C_i^m}{\partial t} + \vec{u}_0 \cdot \nabla C_i^m = D \nabla^2 C_i^m + K_{pm} [C_i^p|_{r=R_1} - C_i^m] \quad (10)$$

$$\frac{\partial C_i^p}{\partial t} + \frac{\partial C_i^s}{\partial t} = D_p \nabla_p^2 C_i^p \quad (11)$$

and

$$\frac{\partial C_i^s}{\partial t} = K_{sp} [f(C_i^p) - C_i^s] \quad (12)$$

where K_{pm} is the kinetic coefficient for mass transfers between the outside and the inside of the pore space, and K_{sp} is the coefficient for mass transfers between the pores and the stationary phase (*i.e.*, the sorbed layer); $u^p = 0$, as the mobile phase is stagnant, and D_p is different from 0, but usually smaller than D_m . We also have in eqn. 11

$$\nabla_p^2 = \frac{\partial^2}{\partial r^2} + \frac{2}{r} \frac{\partial}{\partial r} \quad (13)$$

where r is the radius of the pores in the packing particles.

As the mass of each chemical species is conserved during the separation process, we have

$$\frac{\partial (C_i^m + FC_i^p + FC_i^s)}{\partial t} + \vec{u}_0 \cdot \nabla C_i^m = D \nabla^2 C_i^m \quad (14)$$

From eqns. 10, 14 and 11, we may write

$$K_{pm} [C_i^p|_{r=R_1} - C_i^m] = -FD_p \nabla_p^2 C_i^p \quad (15)$$

As the pores of the packing particles vary widely in size, we prefer to average eqn. 15, which gives

$$K_{pm} (C_i^p|_{r=R_1} - C_i^m) = -F \int_0^{R_1} D_p \nabla_p^2 C_i^p \beta \cdot 4\pi r^2 dr \Big/ \frac{4\pi R_1^3}{3} = -\frac{3D_p F \beta}{R_1} \frac{\partial C_i^p}{\partial r} \Big|_{R_1} \quad (16)$$

where β is the packing porosity (*i.e.*, the internal porosity).

Eqns. 10–12 and 16 are those used for modeling the chromatographic separation of a mixture when mass transfers through pores are taken into account^{4,3}.

The ideal model of chromatography

If the mass transfer processes inside the pores can be neglected, the chromatographic column is operated at a high velocity and the extent of axial dispersion is small, so D is small, while K is large. Thus eqn. 9 becomes, in the case of a single compound

$$\left(1 + F \frac{df}{dC}\right) \frac{\partial C}{\partial t} + u_0 \cdot \frac{\partial C}{\partial x} = 0 \quad (17)$$

Eqn. 17 is the classical hyperbolic conservation law^{4,7}. It is known in mathematics in its canonical form

$$\frac{\partial Q(C)}{\partial t} + \frac{\partial C}{\partial x} = 0 \quad (18)$$

where $Q(C) = (C + Ff)/u_0$.

Lax^{4,7} published a series of landmark papers discussing the hyperbolic conserva-

tion problem in the 1950s. This problem is closely related to the shock theory and is of critical importance for the understanding of the behavior of supersonic aircraft and of nuclear explosions. This problem was given considerable attention at the end of World War II and its investigation led to the book by Courant and Friedrich⁴⁸ and, later, to the papers published by Lax. This later work includes a classical, analytical discussion of the problem in terms of characteristics and functional analysis, and succeeded in deriving a solution of eqn. 18, when $Q(C)$ is a convex function²⁵. The paper also includes a detailed investigation of the conditions under which the numerical calculation of solutions of eqn. 18 can be performed with a computer, and the shock can still be correctly described.

Aris and Amundson²⁵ showed that the propagation of a continuous concentration profile through a chromatographic column can be considered as the result of the propagation of each concentration along a straight line of slope $u_z = u/(1 + df/dC)$, going through the corresponding point of the injection profile. This line is called a characteristic and the velocity u_z associated with a concentration, the characteristic velocity. When two characteristic lines intersect, however, no regular solution of eqn. 17 can exist. A weak solution can be defined^{25,47}, and a concentration discontinuity or shock takes place. The properties of these shocks in chromatography have been recently discussed¹⁰.

In the case of a binary mixture, the ideal model gives the following two equations:

$$\left(1 + F \cdot \frac{\partial f_1}{\partial C_1}\right) \frac{\partial C_1}{\partial t} + F \cdot \frac{\partial f_1}{\partial C_2} \cdot \frac{\partial C_2}{\partial t} + u_0 \cdot \frac{\partial C_1}{\partial x} = 0 \quad (19)$$

and

$$\left(1 + F \cdot \frac{\partial f_2}{\partial C_2}\right) \frac{\partial C_2}{\partial t} + F \cdot \frac{\partial f_2}{\partial C_1} \cdot \frac{\partial C_1}{\partial t} + u_0 \cdot \frac{\partial C_2}{\partial x} = 0 \quad (20)$$

These equations make the classical system of reducible quasi-linear partial differential equations of chromatography²⁵. Their most important property is that the following relationship between the characteristic velocity of each component holds³⁰:

$$u_{z1} = \frac{u_0}{1 + F \cdot \frac{Df_1}{DC_1}} = u_{z2} = \frac{u_0}{1 + F \cdot \frac{Df_2}{DC_2}} \quad (21)$$

where

$$\frac{Df_1}{DC_1} = \frac{\partial f_1}{\partial C_1} + \frac{dC_2}{dC_1} \cdot \frac{\partial f_1}{\partial C_2} \quad (22)$$

and

$$\frac{Df_2}{DC_2} = \frac{\partial f_2}{\partial C_2} + \frac{dC_1}{dC_2} \cdot \frac{\partial f_2}{\partial C_1} \quad (23)$$

In non-linear, high-performance liquid chromatography (HPLC), the elution band profiles are determined essentially by eqn. 18 for a single compound, or by eqns. 19 and 20 for a binary mixture. The solutions of these equations contain self-sharpening parts (fronts or tails, depending on the sign of the isotherm curvature) and continuous parts. It involves an interaction term in the overlapping region of the band, where both components are present. The profile of each component ends abruptly in one point, as there is no axial dispersion.

In most practical cases of interest in HPLC, the molecular diffusion coefficient of the eluates, D_m , is of the order of $1 \cdot 10^{-5} \text{ cm}^2/\text{s}$ and the axial dispersion is of the order of $1 \cdot 10^{-4} \text{ cm}^2/\text{s}$. For low-molecular-weight compounds, the mass transfer coefficient, K , is very large and in most instances, when the diffusion process in the pores is fast, the non-linear behavior of the equilibrium isotherm is the essential factor controlling the band profiles at high concentrations. Accordingly, the solutions of eqns. 18, 19 and 20 are an excellent approximation of the elution band profiles⁸⁻¹⁰. When these assumptions no longer hold, when the dispersion coefficient becomes large (*e.g.*, with columns packed with large particle material), and/or when the mass transfer coefficient becomes small (*e.g.*, with high-molecular-weight compounds, such as proteins), the experimental band profile deviates markedly from the solution of the equation(s) of the ideal model. The extent of this deviation can be estimated by using the singular perturbation method (see below). A more accurate estimate is afforded by computer-calculated numerical solutions, especially at large sample sizes, *i.e.*, when the contribution of the non-linear behavior of the isotherm to the band profile is important⁸. These methods permit the determination of profiles in satisfactory agreement with experimental results^{22,23}. Qualitatively, the effects of a large diffusion coefficient or a small mass transfer coefficient are similar; they contribute to a dispersion term and dampen the self-sharpening process due to the non-linearity of the isotherm⁴⁹.

When the sample size is small and the solute concentrations in the mobile phase are low, the isotherm is nearly, but not quite, linear. The non-linear contribution of the isotherm to the band profile is moderate or small compared with the classical phenomena resulting in band spreading (axial dispersion and resistances to radial mass transfer). The thermodynamic effect can then be treated as a perturbation or as a minor contribution.

These two approaches are discussed in the next section.

Approximate solution in the case of a weakly non-linear behavior

When the contribution of the non-linear behavior of the isotherm to the band profile is small compared with that of the kinetic terms which control normally the band width at the low sample sizes used in analytical chromatography, a perturbation method can be used⁵⁰.

The isotherm can be approximated by its two-term expansion at the origin:

$$f(C) = GC + G'C^2 \quad (24)$$

or, in the case of a binary mixture,

$$f_1(C_1, C_2) = G_1C_1 + G_{11}C_1^2 + G_{12}C_1C_2 \quad (25)$$

and

$$f_2(C_1, C_2) = G_2C_2 + G_{22}C_2^2 + G_{21}C_1C_2 \quad (26)$$

For example, if the actual isotherm is Langmuir:

$$f(C) = \frac{GC}{1 + bC} \quad (27)$$

or, for a binary mixture

$$f_i(C_1, \dots, C_i, \dots) = \frac{G_iC_i}{1 + \sum b_iC_i} \quad i = 1, 2 \quad (28)$$

The coefficients of eqns. 24–26 are related to those of eqns. 27 and 28 by $G' = -Gb$, $G_{11} = -G_1b_1$, $G_{12} = -G_1b_2$, $G_{22} = -G_2b_2$ and $G_{21} = -G_2b_1$.

As the deviation of the isotherm is small in the concentration range investigated, the perturbation method permits the derivation of an approximate solution, which is calculated as a correction to the linear solution due to that non-linear behavior^{50,51}. We write

$$C_i = C_i^0 + C_i' \quad (29)$$

where C_i^0 is the solution corresponding to the linear isotherm and C_i' is the perturbation solution. In the case of a single component, we can use the linear driving force kinetic model (eqns. 4 and 5), which is a convenient first-order approximation when the mass transfer kinetics are fast, but not infinitely so. Writing eqn. 5 as $C_s = f(C) - 1/K\partial f(C)/\partial t$, we obtain

$$(1 + FG) \frac{\partial C'}{\partial t} + u_0 \cdot \frac{\partial C'}{\partial x} - D \cdot \frac{\partial^2 C'}{\partial x^2} = FGb \cdot \frac{\partial C^{02}}{\partial t} + \frac{G}{K} \cdot \frac{\partial^2 C^0}{\partial t^2} \quad (30)$$

where K is a lumped mass transfer coefficient. Eqn. 30 is a linear non-homogeneous first-order partial differential equation. The Green function method can be used to solve it, as discussed in a previous publication⁵⁰.

In the case of the two components of a binary mixture, and within the framework of the ideal model (*i.e.*, assuming the mass transfer kinetics to be infinitely fast and neglecting the axial dispersion), the perturbation equations can be written as

$$(1 + FG_1) \frac{\partial C'_1}{\partial t} + u_0 \cdot \frac{\partial C'_1}{\partial x} = (2FG_1b_1C_1^0 + FG_1b_2C_2^0) \frac{\partial C_1^0}{\partial t} + FG_1b_2C_1^0 \cdot \frac{\partial C_2^0}{\partial t} \quad (31)$$

and

$$(1 + FG_2) \frac{\partial C'_2}{\partial t} + u_0 \cdot \frac{\partial C'_2}{\partial x} = (2FG_2b_2C_2^0 + FG_2b_1C_1^0) \frac{\partial C_2^0}{\partial t} + FG_2b_1C_2^0 \cdot \frac{\partial C_1^0}{\partial t} \quad (32)$$

Eqns. 31 and 32 make a system of linear, non-homogeneous, first-order partial differential equations⁵¹. This system cannot be solved analytically, but the Laplace transform can be used to derive the value of the moments of the perturbed bands. Thus, the variation of the retention time with increasing sample size can be calculated at the onset of the column overload. The results are discussed in a separate publication⁵¹.

The approximation of the Burgers equation

When the concentration of the eluite is small, but is not negligible, the results of the previous, perturbation method are no longer satisfactory and a more sophisticated approach becomes necessary to introduce the effect of the non-linear behavior of the isotherm in the partial differential equation(s) giving the eluite concentration profile. The equilibrium isotherm can still be represented by eqn. 24, however, because the concentration still remains low enough.

In this instance, and if diffusion cannot be ignored, using a variable transform and some approximations, Houghton²⁰ has shown that, in the case of a single component, the chromatography equation can be put under the form of a Burgers equation:

$$\frac{\partial C}{\partial t} + C \cdot \frac{\partial C}{\partial \xi} = D \cdot \frac{\partial^2 C}{\partial \xi^2} \quad (33)$$

where ξ is a function of x , t . Eqn. 33 can be solved analytically, using the Cole-Hopf transform. When the axial dispersion coefficient, D , decreases and approaches zero, the profile predicted by eqn. 33 for the elution profile of a single compound becomes steeper and steeper and tends towards a concentration shock²⁰.

Yeroshenkova *et al.*²¹ and Jaulmes and co-workers^{44,52} have also discussed the transformation of the chromatography equation into a Burgers equation and the properties of the solutions of the latter.

The singular perturbation method

If the non-linear behavior of the band migration process becomes strong, and self-sharpening of one side of the elution profiles takes place, an approximate solution can be searched for by adopting the position opposite to that taken in the previous two sections (*i.e.*, perturbation method and Burgers equation approximation). Instead of considering the non-linear effect of thermodynamic origin as a small perturbation of the linear model, we shall consider the dispersion of kinetic origin as a small perturbation of the ideal model. The small amount of dispersion smoothing out the band profiles predicted by the ideal model can be accounted for as a correction, using the singular perturbation method. This method is a modification of the discontinuous solution, *i.e.*, explains the replacement of the shocks predicted by the ideal model by shock layers, which have a finite width, but propagate at almost the same velocity as a concentration discontinuity.

Goldstein and Murry⁵³ used this method to account for the effect of the mass transfer kinetics on the band profiles.

The stochastic model

The chromatographic process is molecular in nature. At the microscopic level, it is a stochastic process which can be described, *e.g.*, by the Fokker–Planck equation⁴³. The determination of an associated deterministic model permits the calculation of average data, using the classical procedures of the stochastic theory. A discussion of the mechanism of adsorption–desorption as a stochastic process was published long ago by McQuarrie⁵⁴. More recently, Yeroshenkova *et al.*⁵⁵ investigated the effects of the lack of homogeneity of the packing on the column performance.

These last workers derived the following equation relating the packing characteristics:

$$\varepsilon_{\omega}(x)\partial_t C_{\omega} + \mu_{\omega}(x)\partial_t a_{\omega} + w\partial_x C_{\omega} = 0 \quad (34)$$

where ε_{ω} is the packing porosity, μ_{ω} the column volume fraction available to the mobile phase, $\omega \in \Omega$ are the realizations of the possible irregular distributions of the packing in the column which are present in the column and Ω represents the total number of irregular packing distribution which would be made if an infinite number of columns were successively packed; w is the mobile phase velocity and x, t the space and time, respectively. This stochastic model can be reduced to a deterministic one⁵⁵.

The use of the stochastic model could constitute an alternative approach to the study of band profiles and band separation in non-linear chromatography, much as the Monte-Carlo method has been used for the investigation of field flow fractionation⁵⁶.

THEORETICAL ANALYSIS OF SINGLE-COMPONENT NON-LINEAR LIQUID CHROMATOGRAPHY

Although results of practical importance can be derived only from the solution of a two-component problem, as chromatography is a separation process, the solution of the single compound problem, *i.e.*, the accurate prediction of the elution profiles of a rectangular pulse and of the steps injected in frontal analysis is a useful intermediate. From a mathematical point of view, it is a much simpler exercise, because there is only one partial differential equation in the latter case, *versus* two coupled equations in the former. Solutions will be searched first for the single-component problem. In a second step, attempts will be made to extend them to the multi-component problem.

Simulation of the non-linear main part

As mentioned above, when the mass transfer coefficient is very large, the chromatographic behavior and the elution band profile are determined by the main, non-linear part of the model, *i.e.*, the equilibrium isotherm. Accordingly, the solution of eqn. 18 becomes of critical importance.

As shown by the theory of characteristics, each concentration of the injected profile moves on an associated trajectory which in the case of eqn. 18 is a straight line, with a slope $u_z(C)$ in an x, t plane^{10,18,19}. These straight lines are called characteristics. There are two limitations to that statement, however. First, this is possible only as long as the characteristics corresponding to different concentrations on one side of the profile do not intersect. As $u_z = u_0/(1 + F\partial f/\partial C)$, as long as the isotherm is not linear

there will be parts of the injection profiles whose characteristics will intersect^{10,19}. As has been shown, a stable concentration discontinuity or shock forms and propagates¹². The second limitation is that the band spreads because its front moves faster than its tail¹² and the continuous part interacts with the shock and erodes it^{19,31}. Hence the maximum concentration decreases constantly and the band profile cannot be described completely if this interaction is not properly taken into account⁵⁷.

Analytical and numerical solutions can be obtained for eqn. 18. The former are discussed in the next section⁹. Numerical calculations can be performed with a computer, using first- or second-order difference methods⁸. In practice, the first-order, characteristic method is easy to program and gives stable solutions, which have been shown to converge towards the exact solution of eqn. 18 when the integration increments become infinitely small^{58,59}. The Lax-Wendroff, second-order method provides a better accuracy, is more flexible, but much more delicate to handle^{60,61}. With this method, the error caused by numerical dispersion is cancelled in the linear case and markedly reduced in the non-linear case, but numerical instabilities, *i.e.*, oscillations, may take place easily at low values of the axial dispersion coefficient and low values of the time and space increments (see the last section). These spurious artefacts can be avoided only by a careful choice of the values of these increments.

Excellent simulations have been obtained, however, and their results agree well with the corresponding experimental results^{8,22,23,62}.

Retention time under conditions of shock formation

The retention time of the elution band of a pure compound can be derived from previous results published by Aris and Amundson²⁵. The details of the derivation have been published in the case of a Langmuir isotherm, and it has been shown that there is excellent agreement between the predicted and the experimental values^{9,62}. This is due to the fact that, in actual columns, which have a finite efficiency, the shock predicted by the ideal model is replaced by a shock layer^{10,63}. The shock layer has a finite thickness, which increases with increasing column HETP, but propagates at almost exactly the same speed as the concentration shock⁶³. We present here a brief discussion of the solution and a general analysis of the problem¹⁰. We assume that the sample is injected as a rectangular pulse of mass m , width t_p and concentration C_0 .

We can transform eqn. 17 into

$$\frac{\partial C}{\partial t} + \frac{u_0}{1 + F \cdot \frac{\partial f}{\partial C}} \cdot \frac{\partial C}{\partial x} = 0 \quad (35)$$

It is known that the shock velocity is given by^{10,19}

$$U_s = \frac{dx_s}{dt} = \frac{u_0}{1 + F \cdot \frac{f}{C}} \quad (36)$$

In eqn. 36, C is the concentration of the compound in the mobile phase at the shock maximum and f the corresponding value of the isotherm, *i.e.*, the equilibrium

concentration in the stationary phase. When f is convex, the shock takes place on the front of the band profile. Thus, the retention time is the elution time of the shock itself. The migration trajectory of the shock is obtained by integration of eqn. 36. However, we have first to derive a relationship between the concentration of the shock maximum and its position, which describes the constant erosion of the shock during its migration.

The rear side of the band is continuous, as the characteristics associated to each point of this part of the profile diverge like a fan. The velocity associated to a concentration on this part of the profile is given by

$$u_z = \frac{u_0}{1 + F \cdot \frac{\partial f}{\partial C}} \quad (37)$$

At the shock maximum, the continuous part of the profile meets the shock. Both parts of the profile have the same concentration, C_M , and they are at the same location, *i.e.*, $x_s = x_z$. Since the concentration C_M on the continuous part of the profile moves at a constant velocity, given by eqn. 37, we have

$$x_z = u_z(t - t_p) \quad (38)$$

However, as the concentration C_M is also moving with the shock, its velocity at the time considered is given by eqn. 36. Transforming eqns. 36 and 38²⁵, we obtain

$$\frac{d\left(t - t_p - \frac{x}{u_0}\right)}{d\left(\frac{x}{u_0}\right)} = F \cdot \frac{f}{C} \quad (39)$$

and

$$\frac{t - t_p - \frac{x}{u_0}}{\frac{x}{u_0}} = F \cdot \frac{df}{dC} \quad (40)$$

respectively. In eqns. 39 and 40, x is the location of the shock at time t . The function $x(t)$ in this system of differential equations is the trajectory of the shock. Its solution will give the shock retention time, *i.e.*, the time corresponding to the abscissa L . The integration of this set of differential equations can be carried out easily if df/dC is function of f/C ¹⁰. If we have

$$\frac{df}{dC} = \psi\left(\frac{f}{C}\right) \quad (41)$$

we can write

$$\frac{d\left(t - t_p - \frac{x}{u_0}\right)}{d\left(\frac{x}{u_0}\right)} = \psi^{-1}\left(\frac{t - t_p - \frac{x}{u_0}}{\frac{x}{u_0}}\right) \quad (42)$$

Eqn. 42 is a homogeneous differential equation, whose well known solution is

$$\ln\left(\frac{x}{u_0}\right) = \int \frac{d\left[\left(t - t_p - \frac{x}{u_0}\right) / \frac{x}{u_0}\right]}{\psi^{-1}\left[\left(t - t_p - \frac{x}{u_0}\right) / \frac{x}{u_0}\right] - \left[\left(t - t_p - \frac{x}{u_0}\right) / \frac{x}{u_0}\right]} + \text{constant} \quad (43)$$

Eqn. 43, in turn, cannot be integrated for any possible form of $\psi^{-1}(\cdot)$, but only in some special cases.

The function $\psi(\cdot)$, when it exists, is derived from the isotherm. There are a few cases of isotherms for which eqn. 43 can be integrated. For example, when ψ has the following form:

$$\psi(\xi) = \xi^n \quad (44)$$

where n is an integer, hence

$$\psi^{-1}(\xi) = \xi^{\frac{1}{n}} \quad (45)$$

it is possible to integrate eqn. 43 and derive a relationship between x , t and n . Combining eqns. 43 and 44 gives

$$\frac{x}{u_0} = \frac{n}{n-1} \cdot \ln \left[1 - \left(\frac{t - t_p - \frac{x}{u_0}}{\frac{x}{u_0}} \right)^{1 - \frac{1}{n}} \right] + \text{constant} \quad (46)$$

In the case when $n = 1$, which corresponds to a linear isotherm (*i.e.*, $f = \text{constant } C$), eqn. 46 becomes

$$t_r = t_p + t_0(1 + \text{constant}) \quad (47)$$

Eqn. 47 is the classical equation relating the retention time to the slope of a linear isotherm.

In the particular case of $n = 2$, which corresponds to the Langmuir isotherm [$q = aC/(1 + bC)$], eqn. 46 becomes

$$\sqrt{t - t_p - \frac{x}{u_0}} - \sqrt{\frac{Fax}{u_0}} = \text{constant} \quad (48)$$

In this case, the retention time is given by

$$t_r = t_0 \left[1 + Fa \left(1 - \sqrt{\frac{bC_0 t_p}{Fat_0}} \right)^2 \right] \quad (49)$$

where C_0 is the concentration of the injected pulse (*i.e.*, $C_0 t_p F_v$ is the mass of compound injected). For an anti-Langmuir or for the beginning part of an S-shaped isotherm, f is concave. The front part of the band profile is continuous because, in this case, the velocity associated to a concentration decreases with increasing concentration and the characteristics lines fan out. A shock forms on the rear part of the profile, however, and for the same reason. If we assume that the Langmuir equation (eqn. 27), with negative b , still accounts correctly for experimental data (note that the model can be only empirical in such a case, but may still hold in some concentration range), the same procedure as used above leads to the following equation for the retention time of the rear shock:

$$t_r = t_0 \left[1 + Fa \left(1 + \sqrt{\frac{-bC_0 t_p}{Fat_0}} \right)^2 \right] \quad (50)$$

In this case, $b < 0$. Comparison between eqns. 47, 49 and 50 shows that when $b > 0$, the retention time is smaller than in the case of a linear isotherm and decreases with increasing sample size, whereas for $b < 0$ the opposite is true. This result is consistent with that derived from the perturbation analysis, which is valid only at low concentrations⁵⁰.

The continuous part of the profile can be determined knowing the dependence of the velocity associated with a concentration, given by eqn. 37 and the isotherm. As the velocity associated with a given value, C , of the concentration is constant throughout the column, the retention time of that concentration C is

$$t_c = t_p + L/u_z = t_p + t_0 \left(1 + F \cdot \frac{\partial q}{\partial C} \right) \quad (51)$$

Hence the profile is entirely determined by the two equations giving the retention time of the shock and the retention time of the concentrations of the continuous part of the profile. This part of the profile is bound at one end by the retention time of the shock and at the other end by the time corresponding to a zero concentration, *i.e.*, the retention time associated with a linear isotherm^{9,10}.

Coupling between the thermodynamic and kinetic effects

In the case of a single component, the influence on the band profile of the mass transfer coefficient, K , of the diffusion coefficient, D , and of the contribution of the lack of packing homogeneity are similar. In the case of a non-linear isotherm, both mass transfer kinetics and axial dispersion contribute to the broadening of the band profile and to the increase of the thickness of the shock layer⁶¹.

A most important practical problem to discuss now is the extent to which the

axial dispersion term affects the concentration shock predicted by the ideal model. A concentration discontinuity takes place over a distance shorter than a molecular diameter, which is not a very realistic picture. In fact, such a shock constitutes an infinite concentration gradient over a finite concentration range. The corresponding diffusion mass flux would be infinite. A steady-state, dynamic balance must take place between the thermodynamic effect which creates the gradient and the axial dispersion which smooths it out. If the axial dispersion is small enough, the shock is replaced by a shock layer^{10,63}. This is what takes place in most practical cases in preparative chromatography.

In a shock layer, all the concentrations of the part of the profile involved have the same velocity which, for all practical purposes, is equal to the shock velocity⁶³. Rhee and co-workers have published a detailed discussion of the application of the shock layer theory to the determination of the breakthrough curve (frontal analysis profiles) for the single-compound²⁶⁻²⁸ and two-component problems²⁹. However, it seems difficult to extend their analysis to the solution of the pulse injection problem. Thus, an analytical discussion of the properties of the shock layers in elution chromatography has not yet been successfully achieved.

Numerical simulations show that, when the mass transfer coefficient is large, the thickness of the shock layer increases with increasing axial dispersion coefficient⁶³. At low values of the axial dispersion coefficient, the shock layer is very thin and its thickness is proportional to this coefficient. The deviation between the retention time observed and the value predicted by eqn. 49 is of the same order of magnitude as the shock layer thickness^{60,61}. This deviation, and also the thickness of the shock layer, tend towards zero with decreasing value of the dispersion coefficient. When the dispersion coefficient increases, on the other hand, the shock smooths and then disperses at large values of D . In liquid chromatography, the molecular diffusion coefficient is small, usually of the order of $1 \cdot 10^{-5}$ cm²/s, whereas the axial dispersion coefficient (*i.e.*, the ratio $h_m d_p L / 2t_0$, where h_m is the sum $(B/v) + Av^{1/3}$ of the first two terms of the classical Knox plate-height equation⁶⁴, $v = ud_p / D_m$ is the reduced velocity and d_p is the average particle size of the packing material used) is of the order of $1 \cdot 10^{-4}$ cm²/s. With a Langmuir equilibrium isotherm, if the axial dispersion coefficient is increased from a very small to a very high value, the retention time first increases, then goes through a maximum for some intermediate value and eventually decreases towards t_0 .

Similarly, the mass transfer coefficient has an effect on the band profile and, depending on its value, may considerably modify the band profile predicted by the ideal model^{65,66}. For example, if this coefficient is zero, the band moves at the same velocity, $u_0 = L/t_0$, as non-retained compound bands, and, whatever the amount injected, is eluted as a symmetrical band, at $t_r = t_0 = L/u_0$. When the mass transfer coefficient, K , increases, the retention time increases monotonically, from t_0 to $t_r = t_0(1 + FG)$, in the case of a linear isotherm^{49,65,66}. If the isotherm is not linear, the effect is the same as in the linear case at very small values of the mass transfer coefficient. However, $1/K$, which is the resistance to radial mass transfer, acts as a smoothing factor and permits the coupling between the kinetic effects and the non-linear thermodynamic effect. For a given isotherm, the intensity of the self-sharpening of the band increases with increasing value of the mass transfer coefficient, because the smoothing effect of a slow mass transfer kinetics decreases. When K is

large enough, the shock layer appears, its thickness decreases and the band maximum concentration increases with increasing mass transfer coefficient. The shock velocity increases with increasing value of K and the retention time decreases^{49,67}. At very high values of K the retention time reaches a constant limit. In the case of a Langmuir equilibrium isotherm, we observe a characteristic variation of the retention time, which first increases then goes through a maximum and decreases when the mass transfer coefficient increases from zero to infinity. This kind of non-monotonic dependence is characteristic of a non-linear isotherm^{49,67}.

THEORETICAL ANALYSIS OF TWO-COMPONENT NON-LINEAR LIQUID CHROMATOGRAPHY

The ideal model for a two-component mixture is based on eqns. 19 and 20. The hodograph transform is the classical approach to solve these equations, which constitute the reducible quasi-linear partial differential equation system. This transform consists in replacing the functions $C_1(x, t)$ and $C_2(x, t)$ by the inverse functions $x(C_1, C_2)$ and $t(C_1, C_2)$. It turns out that the transformed system of partial differential equations in x and t is linear and can be discussed much more in depth. Thus, the use of the hodograph transform permits a clear discussion of the problem of the separation of a binary mixture.

A theoretical analysis of multi-component adsorption chromatography has been made by Rhee and co-workers for isothermal¹⁸ and adiabatic columns⁶⁸. The use of the simple wave theorems and of the properties of discontinuities were reported.

Two very important cases must be treated separately.

Wide rectangular injection pulse

It can be shown that when the width of the rectangular injection pulse is very large, so large that the plateau of this pulse has not been completely eroded when the band is eluted from the column, the solution of the system of eqns. 19 and 20 is a constant state followed by a simple wave. The theory of non-linear partial differential equations shows that, whenever there is a constant state region within the overlapping area, the neighborhood of such a region is a simple wave region^{25,69}. The simple wave region is a very particular and important region, where there is a constant relationship between C_1 and C_2 , independently of x , *i.e.*, this relationship between the concentrations of the two components remains the same during their migration all along the column.

The constant state corresponds to the elution of the plateau, the simple wave to the elution of both the front and the rear of the band system, adjacent to the constant plateau⁶⁹. In the Langmuir isotherm case, the hodograph plane contains only two straight lines, which intersect at the point corresponding to the constant plateau, *i.e.*, to the composition (C_1^0, C_2^0) of the injection pulse. These two lines are characteristic lines in the hodograph plane.

The solution $C_1(x, t)$, $C_2(x, t)$ can be represented by a graph in an (x, t) plane. Similarly, the transform solution, $x(C_1, C_2)$, $t(C_1, C_2)$, can be represented by a graph in a (C_1, C_2) plane. The transform of the solution from the x, t plane to the C_1, C_2 plane can be considered as a mapping. This mapping is degenerated in both the constant state case and the simple wave case. This means that the mapping results in a decrease

of the number of dimensions of the corresponding space, e.g., from 2 to 1, in which case the plane is mapped into a few lines. Mathematically, the simple wave is defined just by this condition. Obviously, we have then $C_1 = f(C_2)$. The mapping may also result in a decrease of the number of dimensions of the space from 2 to 0, and the entire plane is mapped into a few points, which correspond to the constant state. In both cases

$$J = \left| \frac{\partial(C_1, C_2)}{\partial(x, t)} \right| = 0 \quad (52)$$

Figs. 1–4 show simulated separations, using the computer program described previously⁶¹. This program permits the integration of eqns. 19 and 20, with an apparent diffusion term, of numerical origin, which simulates the finite efficiency of an actual column⁷⁰. Competitive Langmuir isotherms have been used. The mapping of the elution profiles is shown in Figs. 1b–4b. If the injection width is such that the elution profile still has a plateau, as discussed above, this plateau is a constant state for the solution. As shown in Figs. 1–4, the characteristic lines in the C_1, C_2 plane are two straight lines. That with a positive slopes corresponds to the rear part of the elution band in the overlapping region, whereas that with a negative slope corresponds to the front part. It is most important to note that these two straight lines result from the mapping of *the whole band profile of each component, at all positions inside the column*. Fig. 4 shows the band profiles at half length and at the end of a 5 cm long column.

It is remarkable that changes in the value of the dispersion coefficient or the mass transfer coefficient do not change the slope of the characteristic straight lines. They merely affect the range of concentrations during which the characteristic curve is superimposed on these straight lines. The effect is strong on the front part of the elution profile and much smaller on the rear part of the elution profile (see Figs. 1 and 2). When the dispersion coefficient increases and/or the mass transfer coefficient decreases, the range where the simple wave solution is valid decreases (see Fig. 2).

Narrow rectangular injection pulse

In most practical cases, the injection pulse is narrow and the profile of the elution band does not have a constant state. Then, the solutions for the two sides of the elution band cannot be simple waves. The determinant of the Jacobian of the system (see eqn. 52) is no longer zero. Hence the mapping from the x, t plane to the C_1, C_2 plane is not a degenerate mapping. This means that the whole x, t plane is mapped on to the whole C_1, C_2 plane.

In the case of a pulse injection, although the solutions are not simple waves, the following relationship still holds between the concentrations of the two components³⁰:

$$\frac{Dq_1}{DC_1} = \frac{Dq_2}{DC_2} \quad (53)$$

where

$$\frac{Dq_1}{DC_1} = \frac{\partial q_1}{\partial C_1} + \frac{dC_2}{dC_1} \cdot \frac{\partial q_1}{\partial C_2} \quad (54)$$

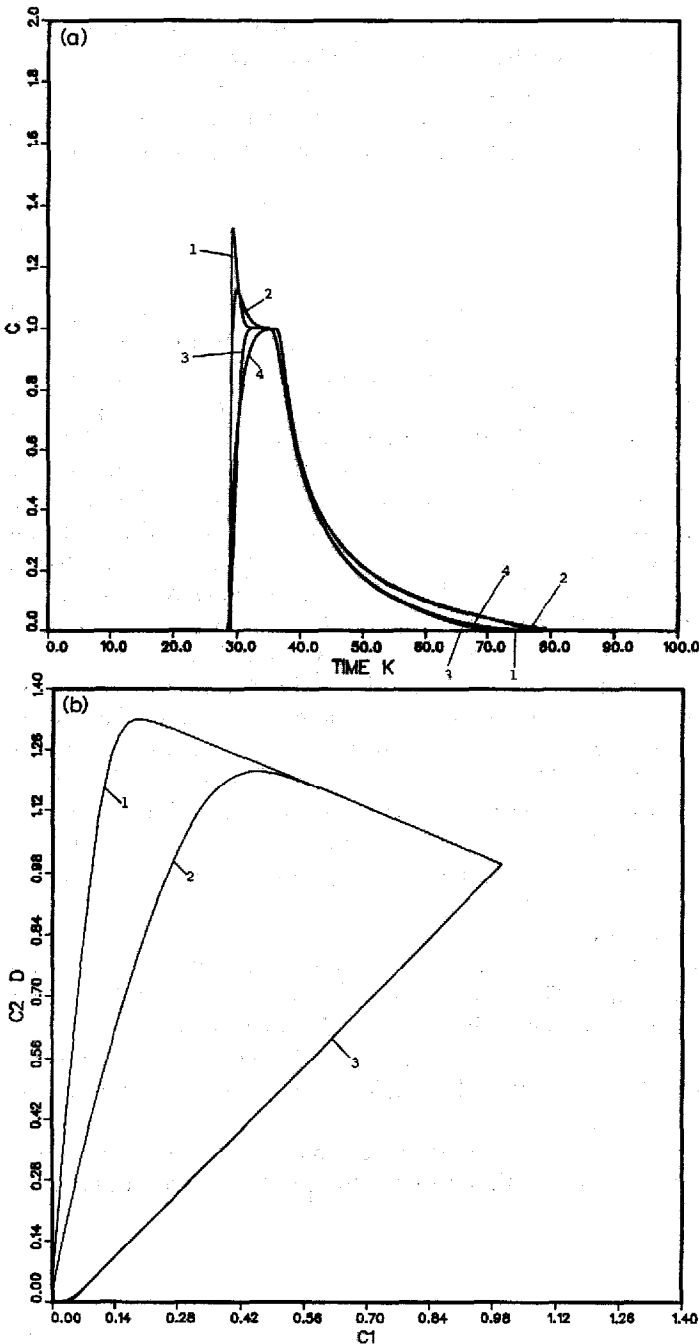


Fig. 1. Numerical simulation of the elution of a wide pulse of a binary mixture and hodograph transform of the chromatogram. Influence of the mass transfer coefficient. Column length, 5 cm; flow velocity, 0.25 cm/s; composition of the mixture, 1:1; concentration of each compound, 1 M ; injection duration, 15 s. Langmuir isotherm coefficients: $a_1 = 8$, $a_2 = 7$, $b_1 = 1$, $b_2 = 2$. Diffusion coefficient: $D = 1 \cdot 10^{-5}$ cm²/s. (a) Two chromatograms are superimposed, corresponding to the injection of the same amount of the same mixture, with two different values of the mass transfer coefficient. Lines 1 and 2, first component; lines 3 and 4, second component. Lines 1 and 3, $K = 25$; lines 2 and 4, $K = 5$. (b) Hodograph transforms of the chromatograms in (a). Line 1 = transform of the front part of chromatograms 1 and 3, until the plateau is reached; line 2 = transform of the front part of chromatograms 2 and 4, until the plateau is reached; line 3 = transform of the rear parts of the two chromatograms.

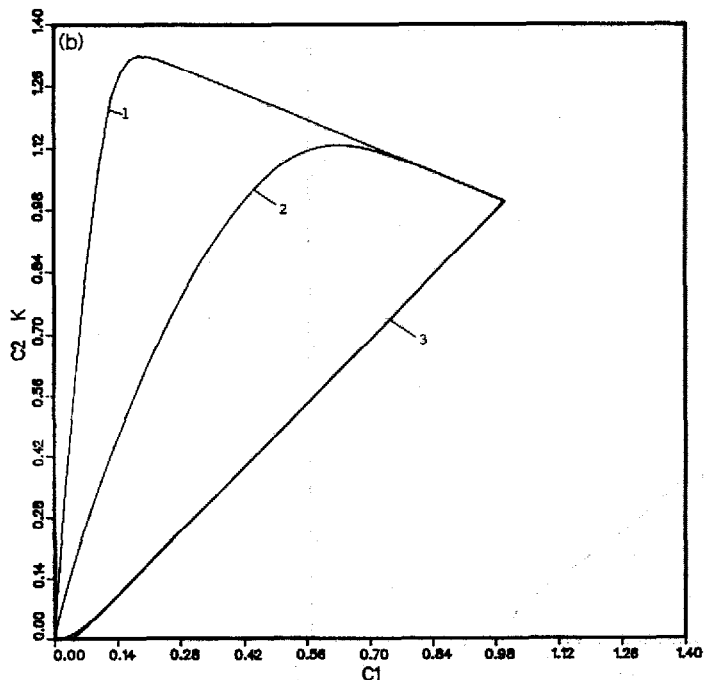
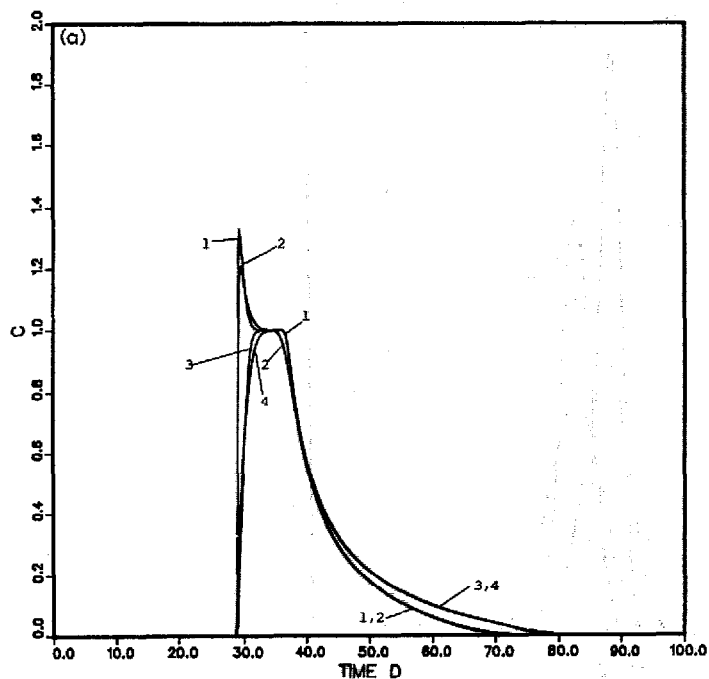


Fig. 2. Numerical simulation of the elution of a wide pulse of a binary mixture and hodograph transform of the chromatogram. Influence of the diffusion coefficient. Same parameters as in Fig. 1, except mass transfer coefficient of both components $K = 25$ and variable diffusion coefficient. (a) The two chromatograms correspond to $D = 1 \cdot 10^{-5}$ (lines 1 and 3) and to $D = 1 \cdot 10^{-3} \text{ cm}^2/\text{s}$ (lines 2 and 4). (b) Hodograph transforms of the chromatograms in (a). Same as for Fig. 1b.

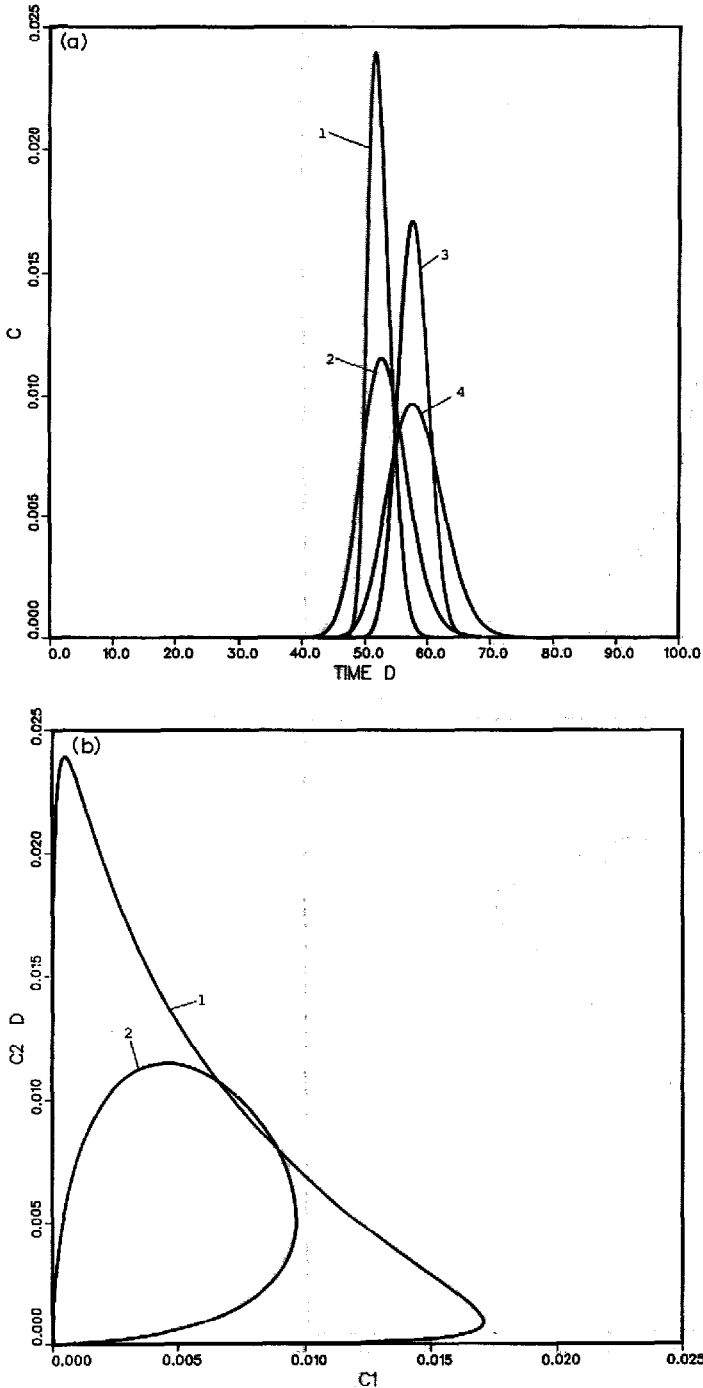


Fig. 3. Numerical simulation of the elution of a narrow pulse of a binary mixture and hodograph transform of the chromatogram. Influence of the diffusion coefficient. (a) Same parameters as for Fig. 2a. except injection duration 0.1 s. Lines 1 and 3, diffusion coefficient $D = 1 \cdot 10^{-5} \text{ cm}^2/\text{s}$; lines 2 and 4, $D = 1 \cdot 10^{-3} \text{ cm}^2/\text{s}$. (b) Hodograph transforms of the chromatograms in (a). Line 1 = profiles 1 and 3; line 2 = profiles 2 and 4.

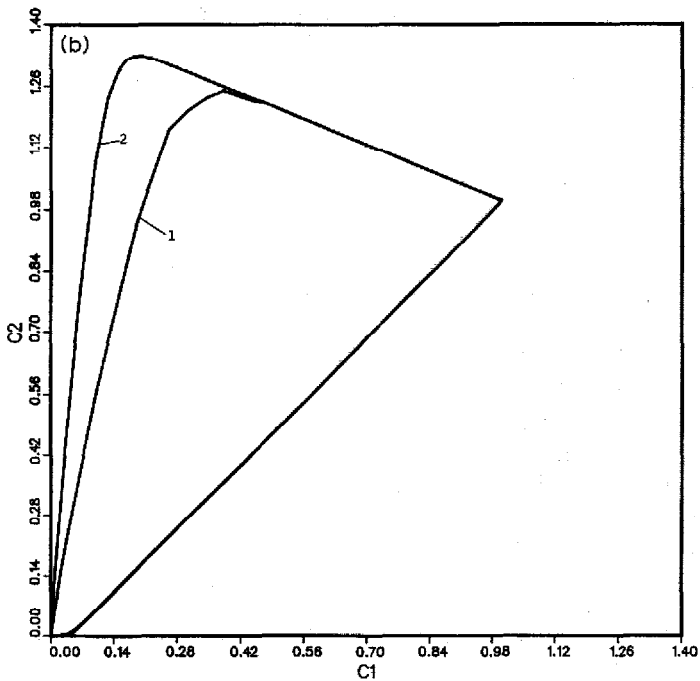
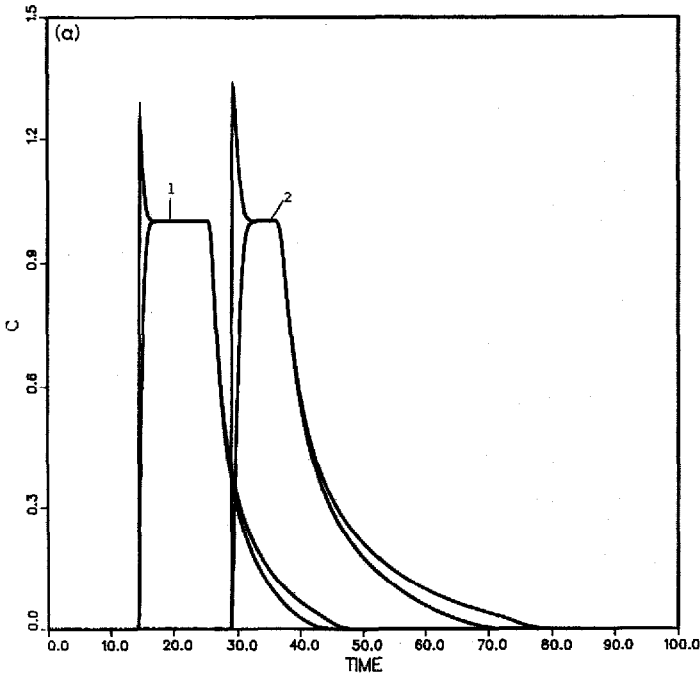


Fig. 4. Numerical simulation of the elution of a wide pulse of a binary mixture and hodograph transform of the chromatogram. Influence of column length. (a) Chromatograms for columns of different lengths: (1) 2.5 cm; (2) 5 cm. Other conditions as in Fig. 1. (b) Hodograph transforms of the chromatograms in Fig. 3a. Line 1 = chromatogram 1; line 2 = chromatogram 2.

and

$$\frac{Dq_2}{DC_2} = \frac{\partial q_2}{\partial C_2} + \frac{dC_1}{dC_2} \cdot \frac{\partial q_2}{\partial C_1} \quad (55)$$

If $q_1 = q_1(C_1, C_2)$ and $q_2 = q_2(C_1, C_2)$ are known, we can derive from eqns. 53–55 the ordinary differential equation for dC_2/dC_1 , and the solutions are two families of curves. If the isotherms, q_1 and q_2 , are Langmuir isotherms, the differential equation is a Clairaut equation and the characteristic lines are two families of straight lines. Thus, in the case of a pulse injection, more than two different values of dC_2/dC_1 exist.

Although in the area where the two bands overlap the concentration profiles of the two bands are such that in each slice the velocities associated with each of the two concentrations are equal ($u_{z,1} = u_{z,2}$), this cannot be true at the edges. In the case of a pulse, the area of the profile must remain constant, so dilution occurs while the band spreads. This causes the progressive redistribution of the equal velocity pairs associated with two concentrations and causes the separation to proceed.

Fig. 3a and b show the elution bands simulated with our program, under conditions where the width of the injected rectangular pulse is narrow. There is no plateau on the elution bands. The corresponding plot in the hodograph plane (C_1, C_2), shows that the derivative $\left. \frac{dC_2}{dC_1} \right|_x$ is not constant in this case. It changes with the position of the zone in the column. The degeneracy is removed.

The influence of the dispersion coefficient and the mass transfer coefficient on the lines in the (C_1, C_2) plane which correspond to a constant value of x is illustrated in Fig. 3. The hodograph transform is now a curve. The lower the column efficiency, the further it is from the coordinate axes.

ERRORS MADE IN THE COMPUTER SIMULATIONS OF THE IDEAL MODEL

Various attempts have been made to generate computer programs permitting the simulation of the behavior of a chromatographic column with various initial and boundary conditions, corresponding to overloaded elution⁸, volume overloaded elution³⁶, frontal analysis²³, displacement⁷¹ and system peaks⁷², for a pure compound or a binary mixture⁷³. In the following discussion, only the case of a pure compound is considered. The investigation of the separation of a binary mixture introduces an additional complexity which is discussed elsewhere⁷⁴.

The main procedures investigated correspond to the integration of eqn. 17 (ideal model) or eqns. 4 and 5 (kinetic model). The results are briefly summarized here. In both cases, the principle of the integration is to replace the continuous (x, t) plane by a grid, ($kh, l\tau$), and to calculate progressively the value of the concentration at each point of the grid, starting from those which are given by the initial and boundary conditions. In practice, profiles along the column [*i.e.*, $C_1(x)$ at successive values of $l\tau$] are calculated and for each profile the couple $l, C_1(L)$ is stored. It is the elution profile.

The characteristic method

Eqn. 18 is replaced by the following finite difference equation:

$$\frac{C_j^{n+1} - C_j^n}{\tau} + u_z \cdot \frac{C_j^n - C_{j-1}^n}{h} = 0 \quad (56)$$

Obviously, a solution of eqn. 56 is not an exact solution of eqn. 18, unless h and τ are infinitely small, which for practical reasons is impossible. The error introduced at each stage can be calculated by replacing each concentration in eqn. 56 by a three-term expansion around C_j^{n70} . The result is

$$\begin{aligned} \frac{C_j^{n+1} - C_j^n}{h} + u_z^{-1} \cdot \frac{C_j^n - C_{j-1}^n}{\tau} &= \\ &= \left(\frac{\partial C}{\partial x}\right)_j^n + u_z^{-1} \left(\frac{\partial C}{\partial t}\right)_j^n + \frac{h}{2} \left(\frac{\partial^2 C}{\partial x^2}\right)_j^n - \frac{\tau u_z^{-1}}{2} \left(\frac{\partial^2 C}{\partial t^2}\right)_j^n = 0 \end{aligned} \quad (57)$$

where $u_z = u_0 \left/ \left(1 + F \cdot \frac{\partial q}{\partial C} \right) \right.$ (see eqn. 17). Eqn. 17 can be rearranged into

$$\frac{\partial C}{\partial x} = -u_z^{-1} \cdot \frac{\partial C}{\partial t} \quad (58)$$

which gives

$$\frac{\partial^2 C}{\partial x^2} = u_z^{-2} \cdot \frac{\partial^2 C}{\partial t^2} \quad (59)$$

Eqn. 57 becomes

$$\left(\frac{\partial C}{\partial x}\right)_j^n + u_z^{-1} \left(\frac{\partial C}{\partial t}\right)_j^n + \frac{h}{2} \left(\frac{\partial^2 C}{\partial x^2}\right)_j^n - \frac{\tau}{2u_z^{-1}} \left(\frac{\partial^2 C}{\partial x^2}\right)_j^n = 0 \quad (60)$$

or

$$\left(\frac{\partial C}{\partial x}\right)_j^n + u_z^{-1} \left(\frac{\partial C}{\partial t}\right)_j^n = \left(\frac{\tau}{2u_z^{-1}} - \frac{h}{2}\right) \left(\frac{\partial^2 C}{\partial x^2}\right)_j^n \quad (61)$$

or, replacing u_z by its value,

$$u_0 \left(\frac{\partial C}{\partial x}\right)_j^n + [1 + Ff'(C)] \left(\frac{\partial C}{\partial t}\right)_j^n = \frac{hu_0}{2} \left(\frac{\tau u_z}{h} - 1\right) \left(\frac{\partial^2 C}{\partial x^2}\right)_j^n \quad (62)$$

If $a = \tau u_z/h = 2$, and $hu_0/2 = D_a$, where D_a is the artificial dispersion coefficient, we have

$$u_0 \cdot \frac{\partial C}{\partial x} + [1 + Ff(C)] \frac{\partial C}{\partial t} = D_a \cdot \frac{\partial^2 C}{\partial x^2} \quad (63)$$

Eqn. 63 indicates that the finite difference eqn. 56 is in fact equivalent to the partial differential eqn. 63. It has been shown by Haarhof and Van der Linde⁷⁵ that eqn. 63 is equivalent to eqns. 4 and 5 (for one compound), when the mass transfer kinetics are fast, and D_a is related to the column efficiency ($D_a = HL/2t_0$). This results assume that the errors which have an order higher than $o(h + \tau)$, *i.e.*, those resulting from the fourth-term expansions in the concentrations in eqn. 56, are neglected.

If we chose the integration increment so that $h = H$, we have

$$D_a = \frac{Hu_0}{2} = \frac{HL}{2t_0} = \frac{\sigma^2}{2t_0} = D_L \quad (64)$$

where D_L is the axial dispersion coefficient for the actual column. Thus, the numerical results derived from eqn. 56 actually contain a dispersion term, and correspond to the behavior of an actual column. They give the solution of a semi-ideal model.

The previous derivation assumes that u_z is constant, which is valid only with a linear isotherm. As in this instance the band profile is Gaussian, this result may seem of limited interest. If u_z is not constant, we write

$$\frac{\partial^2 C}{\partial t^2} = \frac{\partial \left(\frac{-1}{u_z} \right)}{\partial t} \cdot \frac{\partial C}{\partial x} - \left(\frac{1}{u_z} \right) \frac{\partial^2 C}{\partial t \partial x} \quad (65)$$

The difference eqn. 56 is now equivalent to

$$\begin{aligned} u_0 \cdot \frac{\partial C}{\partial x} + [1 + Ff(C)] \frac{\partial C}{\partial t} &= \\ &= D_a \cdot \frac{\partial^2 C}{\partial x^2} - \tau \cdot \frac{\partial^2 f}{\partial C^2} \cdot u_0^2 F \left(\frac{\partial C}{\partial x} \right) / \left(1 + F \cdot \frac{\partial f}{\partial C} \right) \end{aligned} \quad (66)$$

When $\partial^2 f/\partial C^2$ tends towards zero (in which case the isotherm becomes linear), or when $\tau \rightarrow 0$, the analysis is the same as that made in the case when u_z is constant. We must note, however, that this result leaves little freedom to chose the integration increments, since we must keep the Courant number larger than 1, and preferably equal to 2 (see above). Hence, keeping τ small requires also that h be kept small, giving long computing times and a high column efficiency, which is not always the result desired.

The Lax-Wendroff scheme

This is a second-order method, which introduces an axial dispersion term and eliminates the artificial dispersion term, which depends strongly on the space and time

integration increments. Accordingly, this method is more suitable for the calculation of the numerical solutions of multi-component, semi-ideal model, when the range of retention investigated is large.

The system of partial differential eqns. 4 and 5 is replaced by the following finite difference equations:

$$\begin{aligned} \frac{C_j^{n+1} - C_j^n}{\tau} + F \cdot \frac{C_{s,j}^{n+1} - C_{s,j}^n}{\tau} + u \cdot \frac{C_{j+1}^n - C_{j-1}^n}{2h} + \\ - \left(\frac{u_0^2 \tau}{2h^2} + \frac{D}{h^2} \right) (C_{j+1}^n - 2C_j^n + C_{j-1}^n) = 0 \end{aligned} \quad (67)$$

and

$$\frac{C_{s,j}^{n+1} - C_{s,j}^n}{\tau} = K[f(C_j^n) - C_{s,j}^n] \quad (68)$$

The major characteristic of eqn. 67 are the third term, which is a centered difference term instead of $(C_j^n - C_{j-1}^n)/h$, and the introduction in the fourth term of a compensating factor, $u_0^2 \tau / 2h^2$, which cancels out the effect of the artificial dispersion introduced by the integration increments in the characteristic method.

Accordingly, the accuracy of the numerical calculations performed according to eqns. 67 and 68 is much better than that of the calculations made with eqn. 56. The errors made with the Lax-Wendroff scheme are of the order of $o(h^2 + \tau^2)$ in the linear case. The results are nearly totally independent of the values chosen for the time, τ , and the space, h , increments. In the non-linear case, however, additional errors are introduced, which are proportional to τ , but remain nearly independent of the space increment.

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