89. Reformulating the Kinetic Approach of Column Chromatography for a Single Component

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The kinetic model of column chromatography is revisited to explicitly show that this approach yields, when neglecting axial dispersion, a rather simple analytical expression depending only on two dimensionless parameters, namely a dimensionless kinetic retention parameter and a dimensionless time parameter. An expression for the time corresponding to the maximum of the peak is also proposed.

Kinetic approaches of chromatography were first introduced in the forties, and perhaps the best known is the one developed by *van Deemter et al.* in 1956 [1] based on the earlier work of *Lapidus* and *Amundson* [2]. However, from the beginning, mass-transport processes such as diffusion have been considered because, at the early stages of chromatography, a lot of attention was given to the dynamics of zone spreading. A comprehensive overview of the kinetic approach of chromatography was given by *Villermaux* [3] and more recently by *Guiochon* and coworkers [4] [5]. The analytical solutions of the differential equations taking into account diffusion become rapidly complicated and rather intractable when trying to express the concentration distribution. This mathematical complexity has deterred many and, *e.g.*, the so-called *van Deemter* equation is often taught in a simplified parametric way [6].

Neglecting axial diffusion allows the resolution of the differential equation of the kinetic model of chromatography. This approach was first taken in 1944 by *Thomas* [7] to treat ion exchange in a flowing system. In 1953, the solution of the *Thomas* model has been derived by *Goldstein* in the case of a rectangular pulse injection [8] and more recently by *Wade et al.* [9] in the case of *Dirac* injection. In all cases, the resolution of the mass balance and kinetic equations (*cf. Eqns. 2* and *3*, *vide infra*) was achieved using the *Thomas* transformation [9], and the expressions obtained for the concentration distribution profile are rather complicated and too long to be reproduced herein (see Eqn. 22 in [9]).

The purpose of the present paper is to show that the differential equation of the kinetic model of chromatography can be solved in such a way that the resulting expression is similar to that obtained in 1955 by *Giddings* and *Eyring* [10] using a stochastic approach for the concentration distribution in a column of finite length for a *Dirac* impuse injection in the absence of diffusion in the column. We show by the formalism developed below that the concentration distribution can be expressed by a rather simple analytical expression depending on only two independent dimensionless parameters.

The driving force for this investigation stems from our work on liquid/liquid partition chromatography to measure partition coefficients of neutral or ionic drug molecules between water and 1,2-dichloroethane [11] [12]. It is a fact that the kinetic model has inherent limitations which makes it a poor model of preparative and/or nonlinear chromatography. However, in the case of liquid/liquid partition chromatography, the kinetic approach allows direct comparison with other techniques such as voltammetry which can be used to measure the kinetics of the phase-transfer processes [13].

Theory. – Let us consider a chromatography column with a stationary and a mobile phase. We shall consider the retention with a rate constant for solute transfer from the mobile to the stationary phase $\vec{k}$ and a rate constant for release $\overleftarrow{k}$. From the detailed balance principle, the forward and backward rate constants are related by *Eqn. 1* where ΔG_p is the *Gibbs* energy of the 'reaction', *e.g.*, partition between the two phases or adsorption/desorption depending on the chromatographic method. It should be stressed that *Eqn. 1* does not imply that an equilibrium is established between the stationary and the mobile phase.

$$\vec{k} = \vec{k}\exp^{-\Delta G_p/RT} \tag{1}$$

Let L be the length of the column and a the distance between the injector and the beginning of the column as illustrated in *Fig. 1*. We suppose that the linear flow of the mobile phase has a constant velocity v. The differential equations then read as shown in *Eqns. 2* and *3* where c_m and c_s are the concentration of the solute in the mobile and stationary phase, respectively, ϕ the phase ratio, the geometric factor which takes into account the different volume of the two phases, and θ the *Heaviside* step function. By definition, the geometric factor is equal to the ratio of the cross-section area occupied by the stationary and the mobile phases, and it is, therefore, also equal to the ratio of the respective volumes (*Eqn. 4*).

$$\frac{\partial c_m}{\partial t} = -v\frac{\partial c_m}{\partial z} - \vec{k}c_m[\theta(z-a) - \theta(z-L-a)] + \overleftarrow{k}\phi c_s[\theta(z-a) - \theta(z-L-a)] \tag{2}$$

$$\frac{\partial c_s}{\partial t} = \frac{\vec{k}c_m}{\phi}[\theta(z-a) - \theta(z-L-a)] - \overleftarrow{k}c_s[\theta(z-a) - \theta(z-L-a)] \tag{3}$$

$$\phi = \frac{S_s}{S_m} = \frac{V_s}{V_m} \tag{4}$$

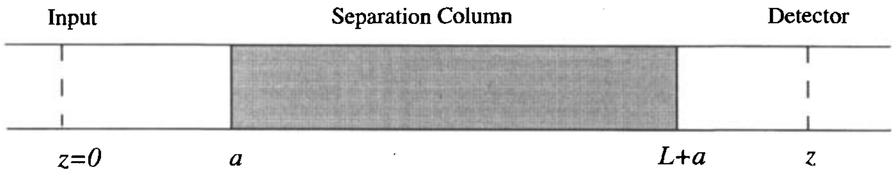

Fig. 1. *Geometric parameters of the chromatographic column*

We assume that the injection corresponds to a *Dirac* impulsion. The boundary conditions for *Eqns. 2* and *3* are then described by *Eqns. 5* and *6*, respectively.

$$c_{\mathrm{m}}(z,0) = c_{\mathrm{o}}\delta(z) \tag{5}$$

$$c_s(z,t) = 0 \quad \text{at} \quad z < a \quad \text{and} \quad z < L + a \tag{6}$$

Eqn. 7 gives the *Laplace* tansform of *Eqn. 2* within the column for $a \leq z < L + a$, and *Eqn. 8* defines $u(s)$. Resolution of *Eqn. 8* yields *Eqn. 9*.

$$v\frac{\partial \bar{c}_{\mathrm{m}}(z,s)}{\partial z} + u(s)\,\bar{c}_{\mathrm{m}}(z,s) = 0 \tag{7}$$

$$u(s) = s + \vec{k} - \frac{\vec{k}\overleftarrow{k}}{s + \overleftarrow{k}} \tag{8}$$

$$\bar{c}_{\mathrm{m}}(z,s) = B(s)\exp^{-\frac{u(s)z}{v}} \tag{9}$$

Outside the column for $z < a$ and for $z > L + a$, the *Laplace* transform of *Eqn. 2* yields *Eqn. 10* for which the solution is given by *Eqn. 11* where $A_<(s)$ and $A_>(s)$ refer to the regions $z < a$ and $z > L + a$, respectively. In the region between the injector and the column, the solution of *Eqn. 11* has the form of *Eqn. 12*, and its *Laplace* transform is, therefore, given by *Eqn. 13* which determines the constant $A_<(s)$ equal to c_0/v.

$$s\bar{c}_{\mathrm{m}}(z,s) = -\,v\frac{\partial \bar{c}_{\mathrm{m}}(z,s)}{\partial z} \tag{10}$$

$$\bar{c}_{\mathrm{m}}(z,s) = A_{<,>}(s)\exp^{-\frac{sz}{v}} \tag{11}$$

$$c_{\mathrm{m}}(z,t) = \frac{c_{\mathrm{o}}}{v}\delta\left(t - \frac{z}{v}\right)\theta(z) \tag{12}$$

$$\bar{c}_{\mathrm{m}}(z,t) = \frac{c_{\mathrm{o}}}{v}\exp^{-\frac{sz}{v}}\theta(z) \tag{13}$$

The continuity of $\bar{c}_{\mathrm{m}}(z,s)$ at $z = a$ and $z = L + a$ allows the calculation of the constants $A_>(s)$ and $B(s)$ by *Eqns. 14* and *15*. In this way, the *Laplace* transform of the concentration in the mobile phase for the section after the column is now given by *Eqn. 16*.

$$A_>(s) = \frac{c_{\mathrm{o}}}{v}\exp^{-\frac{u(s)L}{v}}\exp^{\frac{sL}{v}} \tag{14}$$

$$B(s) = \frac{c_{\mathrm{o}}}{v}\exp^{-\frac{sa}{v}}\exp^{\frac{u(s)a}{v}} \tag{15}$$

$$\bar{c}_{\mathrm{m}}(z,s) = \frac{c_{\mathrm{o}}}{v}\exp^{-\frac{u(s)L}{v}}\exp^{-\frac{s(z-L)}{v}} \tag{16}$$

Eqn. 17 describes the inverse *Laplace* transform of *Eqn. 16* where I_1 is the modified *Bessel* function of the first kind of the first order. The first term of this expression corresponds to the passage of unretained solutes (unrestrained movement of the *Dirac* impulsion), whereas the second term corresponds to the concentration distribution of the retained products. The second term is identical to the expression derived by *Giddings* and *Eyring* [10] from a stochastic approach.

$$c_m(z,t) = \frac{c_o}{v}\theta\left(t-\frac{z}{v}\right)\exp^{-\frac{L\vec{k}}{v}}\delta\left(t-\frac{z}{v}\right) + \frac{c_o}{v}\theta\left(t-\frac{z}{v}\right)\sqrt{\frac{L\vec{k}\overleftarrow{k}}{v\left(t-\frac{z}{v}\right)}}\exp^{-\frac{L\vec{k}}{v}}\exp^{-\left(t-\frac{z}{v}\right)\overleftarrow{k}} I_1\left(2\sqrt{\frac{L\vec{k}\overleftarrow{k}}{v}\left(t-\frac{z}{v}\right)}\right) \tag{17}$$

To illustrate better this analytical solution, let us introduce a dimensionless kinetic retention coefficient ξ and a dimensionless time τ (*Eqn. 18*). The ratio z/v represents the dead time for the passage of a non-retained solute, and the dimensionless time is, therefore, the net retention time normalized by the desorption time $t_d (t_d = \overleftarrow{k}^{-1})$. With this notation, if we omit the first term corresponding to the travelling of the *Dirac* impulsion of which the amplitude decreases exponentially with distance, *Eqn. 17* can be expressed by a rather simple analytical function depending only on the two independent dimensionless parameters defined above and three constants of the system, namely the concentration c_o of the sample, the ratio of the forward and backward rate constants denoted as $K\phi$, and the length L of the column (see *Eqn. 19*). When there is an equilibrium between the stationary and the mobile phase, K represents the distribution coefficient ($K = c_s/c_m$).

$$\xi = \frac{L\vec{k}}{v} \quad \text{and} \quad \tau = \overleftarrow{k}\left(t-\frac{z}{v}\right) > 0 \tag{18}$$

$$c_m(z,t) = \frac{c_o}{LK\phi}\sqrt{\frac{\xi^3}{\tau}}\exp^{-(\xi+\tau)} I_1(2\sqrt{\xi\tau}) \tag{19}$$

Eqn. 19 defines the envelope of chromatographic responses in the absence of axial dispersion, and the results obtained are illustrated in *Fig. 2*. *Eqn. 19* should be compared to previous expressions (*e.g.* Eqn. 22 in [9]) obtained for the same differential equation (*Eqns. 2* and *3*) with the same boundary conditions (*Eqns. 5* and *6*). The only difference between the two formalisms stems from the fact that in liquid/liquid partition chromatography, we do not consider that the stationary phase has a finite concentration of binding sites.

It should be stressed that the apparent simplicity of the *Eqn. 19* stems principally from the choice of the dimensionless parameters ξ and τ, and not from restrictive conditions imposed when solving the differential *Eqns. 2* and *3*.

Maximum of the Distribution. – The maximum of the distribution does not correspond to the first moment (*vide infra*). The time τ_{max} corresponding to this maximum can be obtained by solving *Eqn. 20*

$$0 = \frac{d}{d\tau}\left[\frac{\exp^{-\tau}}{\sqrt{\tau}} I_1(2\sqrt{\xi\tau})\right] \tag{20}$$

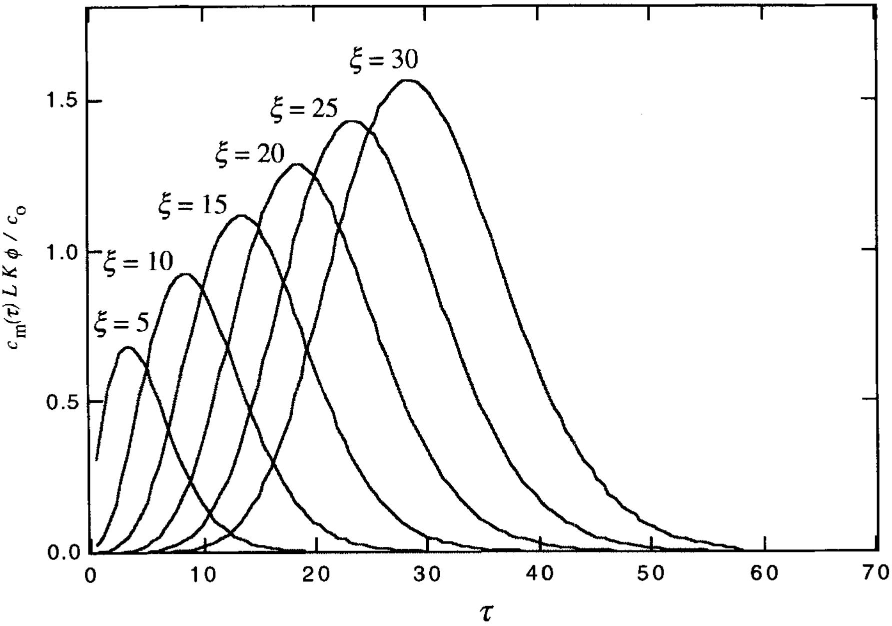

Fig. 2. *Chromatographic response in the absence of axial dispersion derived from* Eqn. 19

Rather than solving directly *Eqn. 20*, we shall give a parametric dependence of τ_{max} on the dimensionless retention coefficient ξ. For that purpose, let us calculate the derivative in *Eqn. 20* and write it as shown in *Eqn. 21*. A change of variables in *Eqn. 21* ($\tau = z^2/4\xi$) yield *Eqn. 22* from which we obtain because $dI_1(z)/dz = I_0(z) - I_1(z)/2$. Using *Eqn. 23* and the definition of ξ according to *Eqn. 18*, we get *Eqn. 24*.

$$\left[1 + \frac{1}{2\tau}\right] I_1(2\sqrt{\xi\tau}) = \frac{d}{d\tau}[I_1(2\sqrt{\xi\tau})] \tag{21}$$

$$\left(1 + \frac{2\xi}{z^2}\right)\frac{dI_1(z)}{dz} = \frac{2\xi}{z} I_1(z) \tag{22}$$

$$\xi = \frac{z}{2} \cdot \left[\frac{I_1(z)}{I_0(z) - (2I_1(z)/z)}\right] \tag{23}$$

$$\tau_{max} = \frac{z^2}{4\xi} \tag{24}$$

Eqns. 23 and *24* give a parametric dependence of the peak maximum on the retention parameter ξ. This allows a direct comparison of the difference between peak maximum and first moment. It is clear that as the chromatographic signal tends towards a *Gaussian* shape ($\xi \to \infty$), the two quantities merge.

Moment of the Distribution. – To calculate the first and second moments of the solute concentration distribution, we shall first normalize the concentration by division by c_0/v

so that the zeroth moment or peak area is equal to unity. The *Laplace* transform of the normalized concentration is then given by *Eqn. 25* and can be developed in series to obtain *Eqn. 26*. By comparison of the definition of the *Laplace* transform of the normalized concentration, we shall be able to obtain directly the moments (*Eqn. 27*).

$$\bar{c}_n(s) = \exp^{-\frac{L\vec{k}}{v}} \exp^{\frac{L}{v}\frac{\vec{k}\overleftarrow{k}}{s+\overleftarrow{k}}} \tag{25}$$

$$\bar{c}_n(\mathrm{s}) = \exp^{-\frac{L\vec{k}}{v}} \exp^{-\frac{L\vec{k}}{v}\left[1-\frac{s}{\overleftarrow{k}}+\left(\frac{s}{\overleftarrow{k}}\right)^2-\dots\right]}$$

$$= 1 - \frac{L\vec{k}}{v}\frac{s}{\overleftarrow{k}} + \frac{L\vec{k}}{v}\left(\frac{s}{\overleftarrow{k}}\right)^2 + \frac{1}{2}\left(\frac{L\vec{k}}{v}\right)^2\left(\frac{s}{\overleftarrow{k}}\right)^2 + \dots \tag{26}$$

$$\bar{c}_n(s) = \int_0^\infty c_n(t)\exp^{-st}\mathrm{d}t = \int_0^\infty c_n(t)\left[1 - st + \frac{1}{2}s^2t^2 - \dots\dots\right]\mathrm{d}t \tag{27}$$

The first moment μ_1 or retention time is then given by *Eqn. 28* where t_d is the mean desorption time. In other words, the dimensionless time corresponding to the first moment is equal to the dimensionless kinetic retention coefficient (*Eqn. 29*). It is clear from *Fig. 2* that the first moment occurs after the peak (*vide supra*). Of course, it is worth remembering that the position of the first moment is a function of the retention property of the column, and is independent of the presence or absence of axial diffusion.

$$\mu_1 = \int_0^\infty t\,c_n(t)\,\mathrm{d}t = t_\mathrm{R} = \frac{L}{v}\frac{\vec{k}}{\overleftarrow{k}} = \xi\,t_\mathrm{d} \tag{28}$$

$$\tau_1 = \xi \tag{29}$$

Similarly, the second moment is defined by *Eqn. 30*. The second central moment which represents the variance is defined by *Eqn. 31* and is, therefore, equal to v_2 given by *Eqn. 32* which corresponds to a dimensionless variance σ_τ^2 (*Eqn. 33*).

$$\mu_2 = \int_0^\infty t^2 c_n(t)\,\mathrm{d}t = \frac{L}{v}\frac{\vec{k}}{\overleftarrow{k}}\left[\frac{2}{\overleftarrow{k}} + \frac{L}{v}\frac{\vec{k}}{\overleftarrow{k}}\right] = \xi\,t_\mathrm{d}^2[2+\xi] = \mu_1^2\left[1+\frac{2}{\xi}\right] \tag{30}$$

$$v_2 = \sigma^2 = \int_0^\infty (t-t_\mathrm{R})^2 c_n(t)\,\mathrm{d}t = \mu_2 - \mu_1^2 \tag{31}$$

$$v_2 = 2\frac{\mu_1^2}{\xi} \tag{32}$$

$$\sigma_\tau^2 = 2\xi \tag{33}$$

This result shows that the dimensionless variance is proportional to the length of the column and inversely proportional to the mobile-phase velocity. Of course, when the concentration distribution tends to a *Gaussian* shape, the band spreading due to the axial dispersion is an additive quantity which can simply be added to the expression obtained above.

When comparing the peak shape with a *Gaussian* curve, it is usual to express the deviation by the skew S (*Eqn. 34*). A positive value of S indicates a tailing of the peak.

The excess E is positive if the distribution is more peaked than a *Gaussian*. It is defined by *Eqn. 35*. It is clear from *Eqns. 34* and *35* that the peak shape tends to a pure *Gaussian* peak when ξ tends to infinity.

$$S = \frac{1}{\sigma^3}\int_0^\infty (t - t_\mathrm{R})^3 c_n(t)\,\mathrm{d}t = \frac{\mu_3 - 3\mu_1\mu_2 + 2\mu_1^3}{\sigma^3} = \frac{3}{\sqrt{2\xi}} \tag{34}$$

$$E = \frac{1}{\sigma^4}\int_0^\infty (t - t_\mathrm{R})^4 c_n(t)\,\mathrm{d}t - 3 = \frac{\mu_4 - 4\mu_1\mu_2 + 6\mu_1^2\mu_2 - 3\mu_1^4}{\sigma^4} = \frac{6}{\xi} \tag{35}$$

In conclusion, this paper presents a rigourous presentation of the kinetic theory of chromatography which yields a rather simple concentration distribution function (*Eqn. 19*) depending, upon only two dimensionless parameters, namely a kinetic retention parameter ξ and a dimensionless time τ.

Furthermore, if we neglect the dead volume between the injector and the column and that between the column and the detector, the kinetic retention parameter is simply defined as the product of the dead time by the first-order rate constant for the transfer from the mobile to the stationary phase (*Eqn. 36*). With the same considerations, the dimensionless time is simply defined as the net retention time normalized by the desorption time (*Eqn. 37*). The first moment is defined when these two dimensionless parameters are equal. All the other parameters relative to the chromatographic signal, *e.g.*, variance, skew, and excess, can be easily described by these two dimensionless numbers.

$$\xi = \frac{L\vec{k}}{v} = t_\mathrm{m}\vec{k} \tag{36}$$

$$\tau = \overleftarrow{k}\left(t - \frac{z}{v}\right) = t_{\mathrm{R},n}\overleftarrow{k} \tag{37}$$

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