

Dispersion in round tubes and its implications for extra-column dispersion

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ABSTRACT

Dispersion in connecting tubing represents a major contribution to extra-column band broadening in liquid chromatography, a factor that is particularly important in miniaturized high-performance liquid chromatographic systems. Although most analyses of extra-column effects are based on the Taylor–Aris theory of dispersion in tubes and the additivity of variances, these approaches are known to be inaccurate under some conditions, but alternative theoretical methods have not been verified experimentally. These aspects have been addressed by a combination of theory and experiment. Experimental elution curves in single tubes are shown to match closely the theoretical predictions based on solutions to the convective diffusion equation, without the need for any adjustable parameters. For tubes in series, use of a convolution relationship allows the accurate prediction of the response of the overall system when radial mixing between the two tubes is present. Although injection and detection systems have not been analysed in detail, they may contribute to discrepancies between theory and experiment if they are not well matched with the remainder of the chromatographic system.

INTRODUCTION

Extra-column contributions to overall peak width in chromatography arise from dispersion in injection and detection systems and in connecting tubing. Such dispersion, which results from the interaction of non-uniform velocity and concentration profiles in the component of interest, reduces the resolution of the separation, and efforts are thus made to minimize it relative to the band spreading occurring in the column itself. A crucial factor in such efforts is minimization of the volume of the extra-column component, but given the continuing development of miniaturized high-performance liquid chromatographic (HPLC) systems, even these endeavours have bounds. Analysis of the extra-column effects then becomes important. Although this in itself obviously does not reduce actual band spreading, it can aid in the analysis of affected data and in the design of components with improved performance characteristics as regards extra-column dispersion.

Most analyses of extra-column contributions to band spreading (*e.g.*, [1,2]) have been based on two assumptions. The first assumption is that the various contributions

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to band spreading are all independent, as a result of which the overall variance is simply the sum of the individual contributions [1,3]. The second refers specifically to dispersion in connecting tubing, where it is generally assumed that the Taylor [4]–Aris [5] result holds, namely that the axial spreading, in terms of the concentration averaged across the tube cross-section, is Fickian, with the dispersion coefficient equal to $u^2 d^2 / 192D$, where u is the average velocity, d the tube diameter and D the solute diffusivity. The Taylor–Aris result predicts that an impulse input of solute will spread such that it always has a Gaussian axial profile.

That both these assumptions are questionable under at least some conditions was recognized by Golay and Atwood [6,7]. They noted that the variances contributed by successive components of the chromatographic system are additive only if there is complete radial mixing at the junction between the components. This is because the input–output relationship for each component is generally expressed in terms of average concentrations, with the implicit assumption that the concentration is, in fact, uniform across the cross-section of the stream concerned.

Golay and Atwood [6] also stressed that, as was clear from the original derivations [4,5], the Taylor–Aris result is valid only for sufficiently long tubes (length $L \gg ud^2/D$). They showed by both computations and experiment that the axial profile of average concentration follows a complex evolution in shape due to the interaction of axial convection and radial diffusion. This evolution, which has been widely documented [6–12], can be summarized as follows. The initial bolus of solute is distorted by the laminar velocity profile into a bullet shape, the length of which increases linearly with time. If the radially averaged concentration is considered, the axial profile adopts a “box-car” [6] shape which, as shown by Taylor [4], decays hyperbolically in concentration with time as it grows in length. The distortion caused by the velocity profile results in steep radial concentration gradients, down which radial diffusion thus occurs. This occurs most visibly near the rear, where solute is mainly in the region of steep velocity gradients near the wall; inward diffusion here gives rise to a bump at the rear of the box-car. At longer times, however, outward diffusion near the snout of the bullet-shaped profile into the slower moving region near the wall also dissipates the front end of the box-car, leading ultimately to the Gaussian profile predicted by the Taylor–Aris theory. Because of the simultaneous decrease in the box-car concentration and increase in the concentration of the Taylor–Aris (dispersion) peak, the elution profile at intermediate times may display a double peak comprising a hyperbolic convection peak followed by a dispersion peak. Such results have been observed experimentally [6,13–16].

Issues such as those outlined above are seldom taken into account in analyses of extra-column dispersion in chromatography, possibly owing in part to the complexity of the behaviour predicted and observed. However, in view of the wide availability of computational power, the routine implementation of more detailed approaches should be possible. It is therefore important to ensure the reliability of the theory in predicting observed experimental behaviour. Similar qualitative trends have been observed in both computational and experimental studies, but direct comparisons of theory and experiment [6,7] have been largely in terms of such parameters as peak variance. The objectives of this work were to perform direct comparisons of experimental data obtained on standard extra-column systems with the predictions of convective diffusion models. Both aspects discussed above, namely the responses of both single tubes and systems consisting of more than one component, are addressed.

THEORY

Dispersion in laminar tube flow

For fully developed laminar flow in a tube the local solute concentration $c(z, r, t)$ satisfies the convective diffusion equation

$$\frac{\partial c}{\partial t} + U \left[1 - \left(\frac{r}{a} \right)^2 \right] \frac{\partial c}{\partial z} = D \left(\frac{1}{r} \cdot \frac{\partial}{\partial r} \cdot r \cdot \frac{\partial c}{\partial r} + \frac{\partial^2 c}{\partial z^2} \right) \quad (1)$$

where U is the centre-line velocity, r , z and t are the radial and axial coordinates and time, respectively, a is the tube radius and D is the solute diffusivity. For the problem of dispersion of a bolus of solute of mass M which is initially uniformly distributed across the tube cross-section, eqn. 1 is to be solved subject to the radial boundary condition

$$\frac{\partial c}{\partial r} = 0 \quad \text{at} \quad r = 0, a \quad (2)$$

denoting symmetry at the centre-line and no flux at the walls, and the initial condition

$$c(z, r, 0) = \frac{M\delta(z)}{\pi a^2} \quad \text{at} \quad t = 0 \quad (3)$$

Two axial boundary conditions are also required in principle; one is the absence of solute in fluid entering the system,

$$c = 0 \quad \text{at} \quad z = 0 \quad (4)$$

while the need for the other falls away because of the solution method used, as discussed below.

This problem has been studied extensively [6–12,17] and a number of solution procedures have been proposed. We have recently reported an approach which is particularly efficient to implement computationally [12]. It is based on the neglect of the axial diffusion term in eqn. 1, thus also eliminating the need for a second axial boundary condition. Omission of the axial diffusion term can be corrected for exactly using a Gaussian smoothing method [18], but this correction is unnecessary for the systems of interest here, as it is important only at very low flow-rates or at extremely short times. As full details of the solution procedure are given elsewhere [12], all that is noted here is that the solution provides values of the dimensionless concentration

$$C = \frac{\pi a^4 U c}{DM} \quad (5)$$

as a function of the dimensionless variables

$$\xi = \frac{r}{a} \quad \tau = \frac{Dt}{a^2} \quad \zeta = \frac{zD}{Ua^2} - \frac{\tau}{2} \quad (6)$$

Thus time is scaled relative to the characteristic time for radial diffusion, while the axial coordinate is transformed such that its origin moves with the mean velocity of the fluid. The solution is independent of any dimensionless parameters, an aspect which is significant in the presentation of computational results and the interpretation of experimental data.

Although the solution procedure provides local concentrations C , it is usually some average concentration that is of interest. The most widely studied average, which is also the one on which the Taylor–Aris result is based, is the straightforward area average.

$$\bar{C} = 2 \int_0^1 C \xi d\xi \quad (7)$$

also referred to as the “slice content” [6,7]. However, as noted by Golay and Atwood [6], a different average is appropriate when the mean concentration in an eluting stream is examined. This average, usually called the cup-mixing average [19], weights the local concentration by the rate at which the fluid emerges from the tube, *i.e.*, by the velocity profile:

$$C_m = 4 \int_0^1 C(1 - \xi^2)\xi d\xi \quad (8)$$

Multiplying the cup-mixing concentration by the mean velocity thus gives the rate at which solute emerges from the tube.

Because averaging eliminates dependence on ξ , \bar{C} and C_m are functions of τ and ζ only. However, elution curves provide concentration data at a fixed value of $z = L$, and this introduces an independent parameter. This quantity is most conveniently expressed in dimensionless terms as a dimensionless minimum transit time (transit time based on the centre-line velocity U), $\tau_m = LD/Ua^2$. The elution curve is then just the value of the relevant average concentration as a function of τ at $\zeta = \tau_m - \frac{1}{2}\tau$. Fig. 1, which shows the predicted cup-mixing responses for a range of τ_m values, illustrates the evolution of the elution curve from an essentially hyperbolic convection peak, through a double-peaked response, to the near-Gaussian Taylor–Aris form where only the dispersion peak is seen.

Response of components in series

The response of a system consisting of multiple components in series is generally obtained by assuming additivity of mean retention times and variances, a result which may be obtained as shown by, for instance, Sternberg [3]. Such results are, however, a consequence of a more general set of results using the theory of residence time distributions or, more generally, age-distribution functions [20,21]. The residence time distribution (RTD) or exit age distribution $E(t)$ gives the distribution of time spent by fluid molecules leaving the system. In principle, it is found by marking all the molecules entering the system at a given instant, and then measuring the fraction of marked

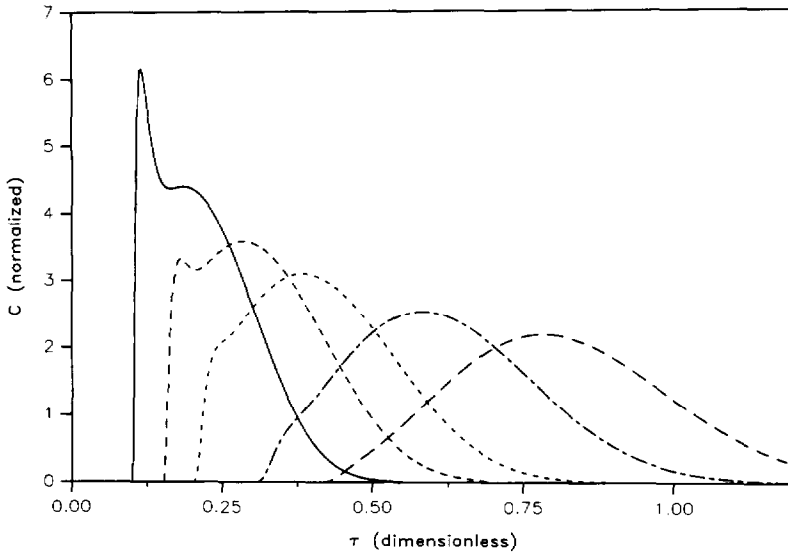


Fig. 1. Evolution of theoretical cup-mixing elution curves as a function dimensionless minimum transit time. τ_m values: —, 0.10; ---, 0.15; -·-, 0.20; - - -, 0.30; — · —, 0.40.

particles which emerge from the system as a function of time. For a solute leaving a chromatographic component, then, $E(t)$ is simply the normalized cup-mixing concentration, measured at the exit, for an experiment in which the input was a perfect impulse. In practice, however, the distinction between cup-mixing and other averages is not always noted, and in fact it is often implicitly assumed that the concentration across the exit is uniform.

There are other implicit assumptions in the use of RTDs which are worth bearing in mind, although they are rarely limiting. One is that of linearity of all components; in chromatography this may cause problems under overload conditions. Another assumption is that components in series are non-interacting, *i.e.*, the RTD of one component is not affected by that of any other. Further, as RTDs are based on the amounts entering or leaving components without regard for spatial inhomogeneities at the entrance and exit, treating components in series assumes that the stream leaving one component is well mixed before it enters another. Atwood and Golay [7] also recognized the need for this requirement for variances to be additive. If all these assumptions are satisfied, the overall RTD for a combination of two components in series can be obtained from the individual RTDs using the convolution equation [20,21]

$$E(t) = \int_0^t E_1(t_1)E_2(t - t_1)dt_1 \quad (9)$$

This relationship can obviously be generalized to one for any number of components in series; it is, in fact, just a particular example of the use of a convolution equation to account for an arbitrary input function (*i.e.*, one other than a perfect impulse).

Using the definitions of the mean residence time

$$\bar{t} = \int_0^{\infty} tE(t)dt \quad (10)$$

and the variance

$$\sigma^2 = \int_0^{\infty} (t - \bar{t})^2 E(t)dt \quad (11)$$

of the RTD, it is easy to show [20,21] by substitution of eqn. 9 that both mean residence times and variances are additive. The more detailed RTD approach is thus consistent with the additivity of mean retention times and variances used ubiquitously in chromatography. The full RTD is used in this work, however, because it allows the full shapes of elution curves to be examined. This is particularly important in the context of extra-column effects, where the responses can be very different in form from the ideal Gaussian shape. This peak shape information can be more informative regarding the nature of extra-column dispersion processes, and it can also provide a more challenging test of model validity in comparisons with real experimental data. The experiments reported later in which two extra-column components were used in series are therefore compared with predictions based on eqn. 9, with the individual component RTDs based on results of the kind shown in Fig. 1.

EXPERIMENTAL

The aim of the experiments performed was to obtain solute response curves for impulse injections into components both individually and in series. The components of interest were simply straight sections of tubing of various dimensions, as discussed in more detail below, to allow comparison with the responses predicted using the theory outlined above. The experimental system was thus selected so as to match closely the idealized conditions on which the models are based.

As pressure drops in open tubes are relatively low, a Harvard Apparatus (South Natick, MA, USA) Model 909 syringe pump was used as the primary source of solvent under pressure. A syringe pump has the advantage of delivering steady flows without pulsation, unlike the delivery from a high-pressure dual-piston HPLC pump. However, to evaluate the effect of flow pulsation under standard chromatographic conditions, a Waters Assoc. (Milford, MA, USA) Model 6000 HPLC pump was also used and results were compared with the syringe pump results. Both pumps were calibrated by volume collection over a fixed period to time, but owing to differences in control of the two pumps, discrepancies of up to about 2% in the flow-rates for corresponding experiments were possible.

The injection valve was chosen so as to approach the impulse input condition in eqn. 3. A Rheodyne (Cotati, CA, USA) Model 7520 valve with a 0.5- μ l injection passage on the stator was used. Detection was accomplished using an Isco (Lincoln,

TABLE I
TEST COMPONENT PARAMETERS

System	Diameter (cm)	Length (cm)	Volume (μ l)	Diffusion time, a^2/D (s)
A	0.025	100.0	50.7	19.7
B	0.051	100.0	202.7	78.7
C	0.102	100.0	810.7	314.7
D	0.051	158.8	321.9	78.7

NE, USA) Model V4 UV-visible absorbance detector with computerized data acquisition and a response time as low as 0.05 s. The flow cell was a standard Z-pattern type with an illuminated volume of 1 μ l and a path length of 0.5 cm. The connecting tubing joining the test section to the flow cell was 0.013 cm in diameter and about 10 cm long. Hence the volume of the injection and detection system was small enough (a few μ l) that its effect on \bar{t} and σ^2 was small, both in absolute terms and relative to the contributions of the test sections themselves.

The test components were cylindrical tubes of various diameters, purchased precut from Upchurch Scientific (Oak Harbor, WA, USA). Four different geometries were examined, as shown in Table I. For each set, the tube volume and the diffusion time scale a^2/D are also shown. The effect of placing components in series was examined in two ways, each for two pieces of tubing of equal length with the same combined length as shown in Table I. First, interaction of components without radial mixing was studied by using a zero dead volume connector (Alltech, Deerfield, IL, USA), intended to make two tubes in series behave as a single tube with the same overall length. Second, forced convective radial mixing was introduced by including a stainless-steel precolumn filter (Model A315; Upchurch Scientific) in the junction between components.

Benzyl alcohol (Aldrich, Milwaukee, WI, USA) was used as the solute and distilled, de-ionized water as the solvent. The binary diffusivity of benzyl alcohol in water has been measured experimentally as $0.82 \cdot 10^{-5}$ cm²/s at 20°C, a value which is within less than 10% of the values predicted by three widely used equations for estimating diffusivities in liquids [22]. Detection was at the maximum absorbance wavelength, namely 252 nm.

RESULTS AND DISCUSSION

Single tubes

The experimental system was intended to approximate as closely as possible the model system described by eqns. 1–4. However, as more than one approach to averaging is possible, as is illustrated by eqns. 7 and 8, it is important to base comparisons between theory and experiment on the appropriate average. For the type of detector used here, in which the optical path is axial, the area-average concentration is clearly inappropriate. As discussed by Atwood and Golay [7], the cup-mixing is, strictly speaking, also inappropriate. There is, however, good reason to expect the cup-average to provide a reasonable approximation to the measured results. As the

Z pattern of the detector flow cell disrupts the laminar flow sufficiently to induce mixing of the stream entering the cell, the solute flux into the cell (product of volumetric flow-rate and concentration) should be determined by the cup-mixing, and not the area-average concentration. Further, as the volume of the flow cell is much smaller than that of the dispersive components being tested, the measured concentration will be only weakly dependent on flow cell characteristics relative to its dependence on the concentration in the entering stream.

Fig. 2 shows a comparison of normalized experimental elution curves for each of the two pumps with theoretical results for the cup-mixing and area-average concentration for a system with $\tau_m = 0.163$ (system D in Table I). The results here and in subsequent figures are presented with τ as the independent variable, *i.e.*, with time scaled by the diffusion time a^2/D , to allow subsequent comparison of multiple experimental systems on a single plot; real time scales can be recovered using the a^2/D values shown for each system in Table I. The cup-mixing concentration profile in Fig. 2 is clearly closer to the experimentally observed curves than is the mean concentration; it should be emphasized that the theoretical curves were found with no adjustable parameters. All comparisons shown below are thus with the computed cup-mixing concentration. It is interesting that experimental results obtained using a detector measuring absorbance across a cross-section of the tube [16] show better agreement with the theoretical curves for the mean concentration than for the cup-mixing concentration. In Fig. 2, the difference in behaviour between the experiments with different pumps is negligible. Most of the experimental curves below were obtained with the syringe pump, but in some cases the HPLC pump was used.

Figs. 3–6 show experimental and computed elution profiles for τ_m values of 0.108, 0.163, 0.218 and 0.447, respectively. In each instance except the first, experimental curves are shown for the four different tube geometries listed in Table I,

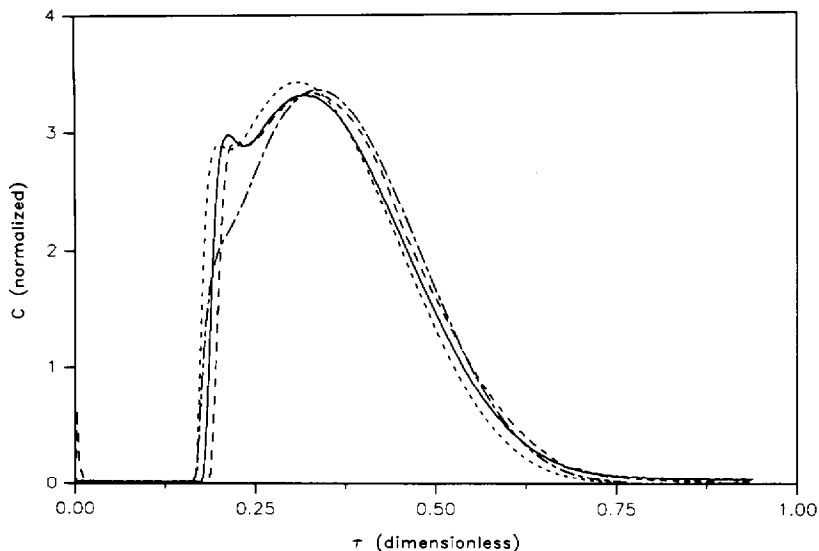


Fig. 2. Comparison of theoretical and experimental elution curves for single tube (system D) with $\tau_m = 0.163$. Experimental: —, syringe pump; ---, HPLC pump. Theoretical: - · -, cup mixing; — — —, area average.

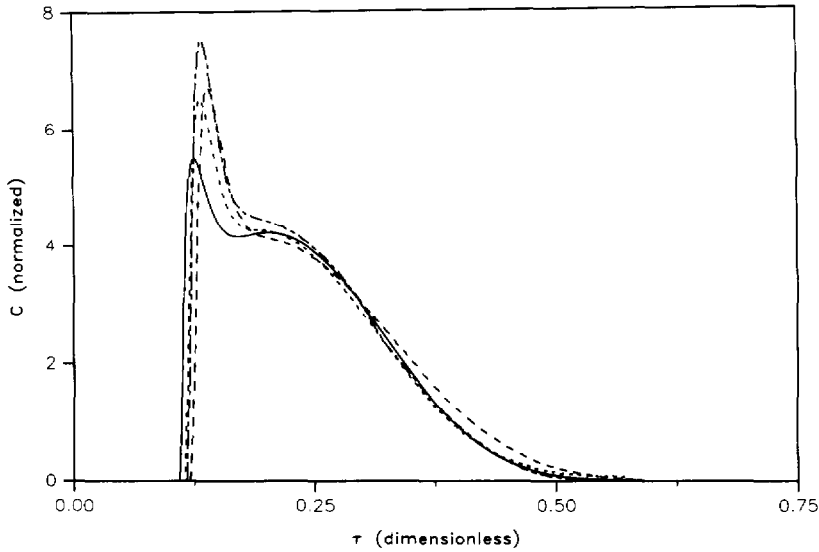


Fig. 3. Comparison of theoretical and experimental elution curves for single tubes of different geometries with $\tau_m = 0.108$. Experimental: ---, B; --, C; ---, D; —, theoretical.

with the appropriate τ_m value attained for different tubes by adjusting the flow rate. Although only one experimental curve is shown for each set of parameters, each experiment was replicated several times; the curves are highly reproducible, the only significant variation being that resulting from errors in recording the injection time. These errors, which were a consequence of using a manual injection valve and thus

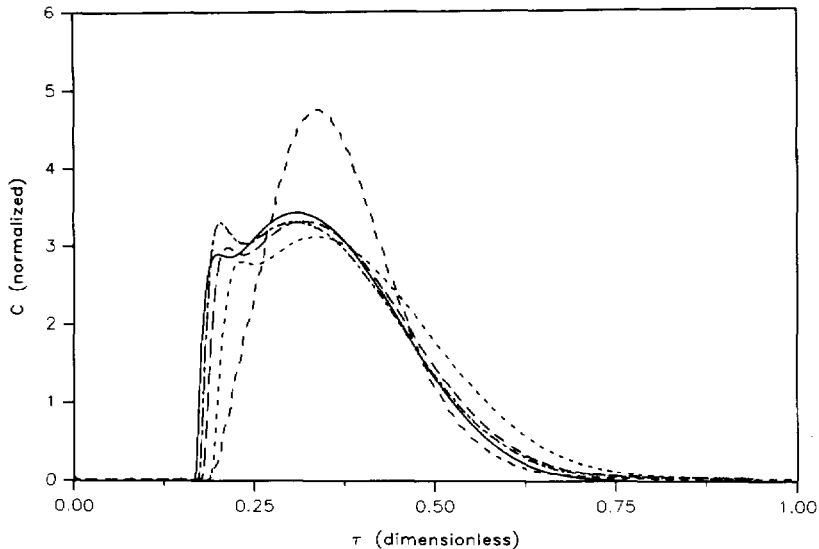


Fig. 4. Comparison of theoretical and experimental elution curves for single tubes of different geometries with $\tau_m = 0.163$. Experimental: ---, A; --, B; ---, C; —, D; —, theoretical.

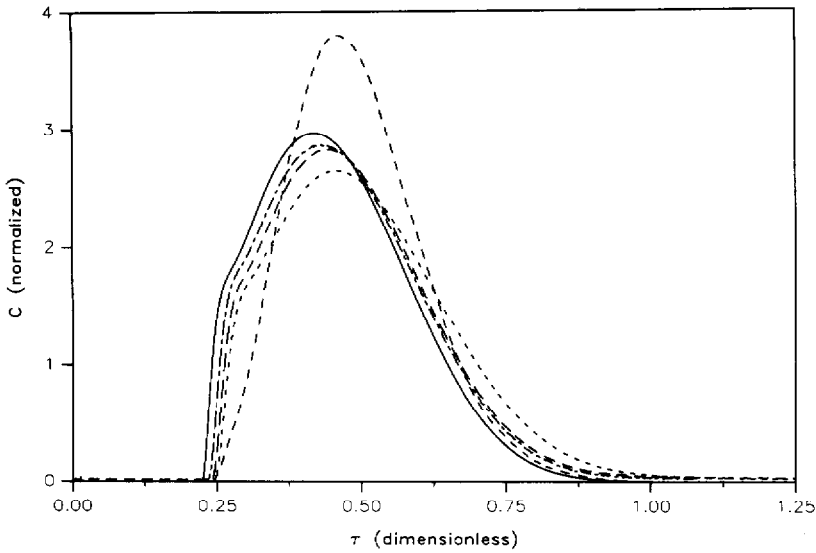


Fig. 5. Comparison of theoretical and experimental elution curves for single tubes of different geometries with $\tau_m = 0.218$. Lines as in Fig. 4.

were less than 1 s, are also the main reason for the shifts among the different curves on the plots. They become less noticeable at larger τ_m values as the time scales of the experiments increase. Agreement between theoretical and experimental curve shapes is generally excellent, especially considering, as noted previously, that the theoretical

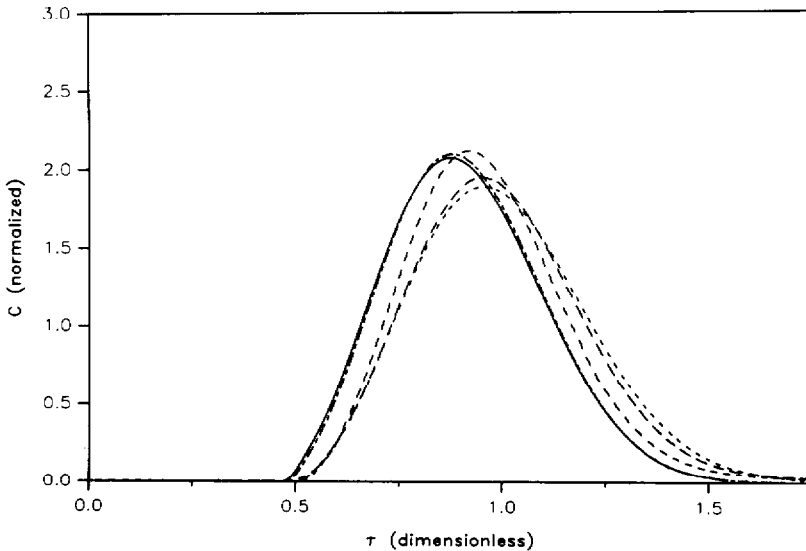


Fig. 6. Comparison of theoretical and experimental elution curves for single tubes of different geometries with $\tau_m = 0.447$. Lines as in Fig. 4.

computations involve no adjustable parameters. Agreement is poorest for system A, where the test-component volume is smallest, and the response is thus most likely to be significantly affected by transport in the injection and detection system. This is why a result for system A is not shown in Fig. 3, where the minimum transit time would be about 2 s. It is interesting, however, that in Fig. 4 the system A elution peak is of approximately the same width as predicted by theory.

A discrepancy between theory and experiment seen for small τ_m (Fig. 3, and system C result in Fig. 4) is that the experimental convective peaks are sharper than predicted by theory. A change of the order of 10% in τ_m would be sufficient to bring the theoretical curve into better agreement, but a more likely explanation for the discrepancy is one recognizing the nature of the injection. As noted previously, the injection valve tubing is in line with the test section. However, the former is of only 0.013 cm diameter, *i.e.*, smaller than any tubing used as a test section. Consequently, the injection may be biased toward the centre of the tube used as test section, instead of the uniform distribution denoted by eqn. 3. As the convection peak arises from material initially near the tube centre, an enlarged convection peak may result from the non-uniform initial distribution. That the widest tubing (system C) is the only one affected in Fig. 4 would appear to support this conjecture.

Tubes in series

The experiments to investigate interacting components in series were based on essentially the same systems for which results are shown in Figs. 3–6, the key difference being that each tube now consisted of two parts of equal length. These two parts were connected by either a zero dead volume fitting to minimize radial mixing or by an in-line solvent filter to maximize it. Fig. 7 shows a comparison of experimental and theoretical results for system B for the two linkage modes, for an overall τ_m of 0.163;

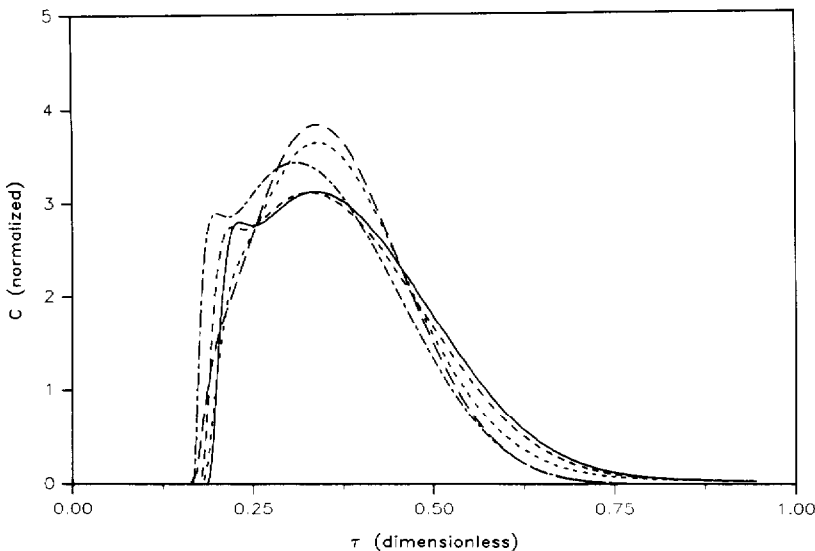


Fig. 7. Comparison of theoretical and experimental elution curves for system B with $\tau_m = 0.163$, showing effect of various tube configurations. Experimental: —, single tube; - - -, two tubes with zero dead volume connector; - · - ·, two tubes with filter. Theoretical: - - - -, single tube; — — —, convolution.

the corresponding single-tube experimental result is also shown for reference. Theoretical curves are shown for the convolution of two tubes (eqn. 9) and for a single tube of the same total length.

For the zero dead volume fitting, the response is very similar to the theoretical and experimental curves for a single tube. On the other hand, the convolution approach appears to allow the overall response to be calculated fairly accurately for the system incorporating the in-line filter between the two tubes, at least in the example shown. Both the theoretical and experimental curves here are significantly smoother than in the absence of mixing, and it is also noticeable that the standard parameters used to characterize response peaks, such as variances, peak widths at various ordinate values, etc., may be misleading regarding the nature of the responses. However, it follows from the accuracy of the convolution result that the overall variance of the response is equal to the sum of the two contributing variances, as is generally assumed in practice.

Additional comparisons of responses with the in-line filter are shown in Figs. 8–10 for three different τ_m values; the system A response is omitted from Fig. 8 for the same reason as in the corresponding single-tube case. Agreement between theory and experiment is again excellent for larger τ_m values, but for small τ_m , as in Fig. 8, the experimental curves display features such as convection peaks which are more characteristic of systems without mixing. This could be due to the steeper radial concentration gradients at small τ_m , making good radial mixing at the junction more difficult. As the nature of the mixing process due to the filter is poorly understood, it is not clear what the effect is of the higher rates used to attain small transit times. Here, as in Fig. 4 discussed above, it is again the widest tubing that appears most susceptible to enlargement of the convection peak, again supporting the suggestion that inadequate radial transport is involved.

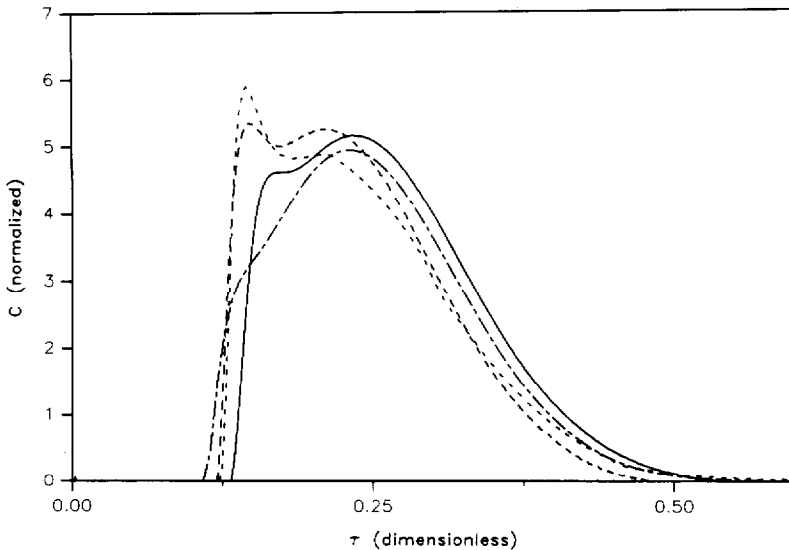


Fig. 8. Comparison of theoretical and experimental elution curves for tubes in series with $\tau_m = 0.108$. Experimental: --, B; - -, C; ---, D. —, Theoretical (convolution).

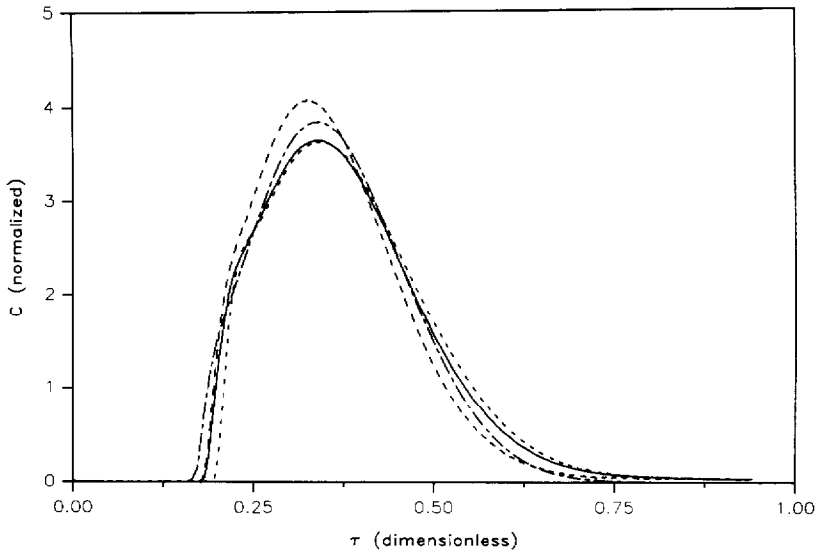


Fig. 9. Comparison of theoretical and experimental elution curves for tubes in series with $\tau_m = 0.163$. Lines as in Fig. 8.

CONCLUSIONS

Two issues concerning the modelling of extra-column dispersion have been addressed. First, we have shown that it is possible to predict the shape of elution peaks for single tubes fairly accurately, without the need for adjustable parameters. These

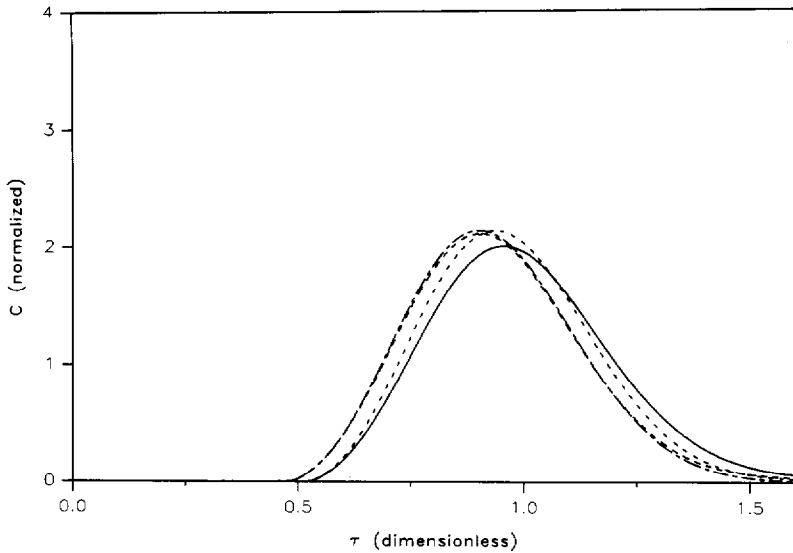


Fig. 10. Comparison of theoretical and experimental elution curves for tubes in series with $\tau_m = 0.447$. Lines as in Fig. 8.

peaks are different in shape from those predicted by the widely used Taylor–Aris theory, which is unlikely to be adequate for the tube geometries most frequently used in chromatographic practice.

The second issue addressed was that of predicting elution curves from a system consisting of multiple components in series. When radial mixing between components is adequate, the convolution approach allows the individual RTDs to be combined fairly accurately, so that under these conditions variances should indeed be additive, as is usually assumed. Although the convolution approach proved to be inaccurate in some systems studied here, only relatively poor radial mixing could be accomplished under the conditions studied; the lateral mixing occurring naturally during flow through a packed columns should help to justify the assumption of additivity of variances in actual chromatographic systems. However, it is important that the proper approach be used to find the variances of the individual components, especially the connecting tubing. Another consequence under conditions where convolution is warranted is that much of the “fine structure” of the individual elution curves, such as convection peaks, is smoothed out by the convolution process, so that anomalous peaks are unlikely to arise due to extra-column effects under normal chromatographic conditions.

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