On the apparent dispersion coefficient of the equilibrium dispersion model: An asymptotic analysis

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ABSTRACT

To model chromatography, researchers have developed several approaches. These cover a broad range of applications and, depending on the assumptions adopted, have different levels of accuracy. In general, the most suitable modelling approach is the simplest that can describe a process with the desired accuracy. A model that often meets this criterion is the equilibrium dispersion model (EDM). This features one mass balance equation per analyte, including an axial dispersion term, and assumes the analyte concentrations in the mobile and stationary phases to be in local equilibrium. To account for the finite mass transfer rate between the phases, the model employs an *apparent* dispersion coefficient. Two expressions are available for this coefficient, one being used much more frequently than the other. In this paper, we aimed to clarify which one should be favoured. A desirable feature of simple models is that they can be derived from more general ones with appropriate physical assumptions and rigorous mathematical methods. Thus, to answer our research question, we derived the EDM from the more general pore diffusion model (POR), using an asymptotic method. The expression obtained for the apparent dispersion coefficient does agree with one of the two reported in the literature – the less frequently used. To test the validity of this expression, we simulated elution profiles using the two versions of the EDM and compared the results against those from the POR model. The simulations were conducted in the range where the POR and EDM models should be essentially equivalent, their results confirming the outcome of the asymptotic analysis. This work offers a solid theoretical grounding for the EDM, clarifies which formulation of the model is correct, and provides usable applicability conditions for the model.

1. Introduction

Chromatography is one of the most common techniques for analyzing and purifying fine chemicals and drug compounds. Because the increase in computational power has allowed the in-silico design and optimization of the process, for many years developing chromatography models has been of critical interest. Many models of different accuracy and complexity have been proposed. In general, the model that should be favoured is the simplest one that can describe a process with the desired accuracy; this is particularly important for industrial applications, where simulations must describe the behaviour of actual chromatography units sufficiently well, but computational time must be minimized.

The most detailed chromatography model is known as *general rate model* (GRM) [1–7]. This accounts for the physical phenomena of adsorption-desorption, pore surface diffusion and pore bulk diffusion within the stationary phase, of mass transfer between the stationary and mobile phases, and of convection and fluid dynamic dispersion within the mobile phase. If adsorption and desorption can be regarded as infinitely fast, then in every location inside the stationary phase the analyte concentration in the bulk of the pores can be assumed to be in equilibrium with the analyte concentration on the surface of the pores; therefore, an adsorption isotherm can be used in lieu of rate equations for the adsorption and desorption processes. In addition, often it is assumed that pore surface diffusion is negligible, so that only bulk diffusion in the pores of the stationary phase is considered [8,9]. But even with these simplifying assumptions, the GRM is rarely used in industrial applications, because it is computationally expensive and contains too many unknown parameters whose estimation is complex and time-consuming, requiring significant extra experimental work in the early stages of process development.

To find simpler models, researchers often describe the stationary phase in terms of analyte concentrations averaged over the volume of stationary phase present between two infinitesimally close cross-sections of the chromatography column. In this approach, one does not

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account for the variation of concentration within the particles forming the stationary phase; but to account for the mass transfer resistance within the particles, one replaces the coefficient of mass transfer between the surface of the particles and the bulk of the mobile phase with an *effective* mass transfer coefficient that lumps the internal (to the particles) and external mass transfer resistances [9–11]. In the stationary and mobile phases, the evolution in time and space of the analyte concentrations are governed by a set of two differential mass balance equations per analyte, and in the mobile phase dispersion effects are formulated via an axial dispersion coefficient that depends *only on the fluid dynamics* within the column [12–15]. Various authors refer to this model as *lumped pore diffusion model*, using the acronym POR [11,16–19], but others refer to it as *transport dispersion model* (TDM) (e.g., [9,20,21]).

An even simpler model, frequently used for industrial applications, is known as *equilibrium dispersion model* (EDM). In addition to all the assumptions reported above, the EDM also assumes that (at every axial location in the column) the analyte concentrations in the mobile and stationary phases are in equilibrium, so that they may be related via adsorption isotherms. As a consequence, the EDM features only one differential mass balance equation per analyte. The equilibrium relations between the analyte concentrations in the two phases would rigorously hold if the rate of mass transfer between the phases were infinite; since this is never the case, to account for the finite rate of mass transfer, the model employs an *apparent* dispersion coefficient [9–11,19,22–28]. Usually, this coefficient is modeled as the sum of the fluid dynamic axial dispersion coefficient, which features in the POR model, and a corrective term that accounts for the mass transfer effects between the two phases.

The apparent dispersion coefficient can be calculated either with Van Deemter plots [23] or with equations that involve parameters related to fluid dynamics, mass transfer and adsorption isotherms [11,19,24,29,30]. These equations were obtained through the method of moments analysis [10,11,31–33]. In this method, Laplace transforms are used to solve the chromatographic models analytically. Using the solutions in the Laplace domain, one can then derive analytical expressions for the temporal moments of the analyte concentration profiles, quantities that are closely related to important properties of the elution profiles, such as retention time, band broadening, front asymmetry and kurtosis. Expressions for the apparent dispersion coefficient can then be obtained by matching the second central moment of the EDM with that of the GRM. This procedure is thoroughly outlined in the article by Qamar et al. [33].

In the literature, two equations are available for the apparent dispersion coefficient, and even if they may seem similar, they do yield quite different predictions. In this work, we aimed to determine which expression should be favoured. To do this, we *derived* the EDM – along with the analytical expression for the apparent dispersion coefficient – from the more general POR model by applying an asymptotic method [34]. The advantage of this approach is that not only does it allow deriving the EDM via rigorous mathematical passages, but it also yields the conditions under which the model can be used. Encouragingly, the resulting expression for the apparent dispersion coefficient coincides with one of the two expressions reported in the literature – but interestingly it is the expression that appears to be used far less frequently. To test the validity of our findings and the accuracy of the two expressions, we simulated a chromatographic separation using the POR model (regarded as benchmark) and the two versions of the EDM, under conditions where the models should be virtually equivalent.

The paper is organized as follows. In Section 2, we briefly present the POR and EDM models, along with the expressions for the apparent dispersion coefficient. In Section 3, starting from the POR model, we derive the EDM using perturbation theory. In Section 4, we simulate a chromatographic separation using the POR model and the two versions of the EDM, comparing and discussing the results. In Section 5, we summarize our findings and conclude the work.

2. The POR and EDM models

Both models assume that adsorption and desorption are infinitely fast and pore surface diffusion is negligible. Moreover, they both describe the stationary phase in terms of mean analyte concentrations, without capturing the concentration changes inside the particles that form the stationary phase. As said, to account for the mass transfer resistance within the particles, both models replace the mass transfer coefficient between the surface of the particles and the bulk of the mobile phase with an *effective* mass transfer coefficient that lumps internal and external mass transfer resistances. For each analyte, both models consider three concentration terms: the concentration c_1 in the bulk of the mobile phase, the concentration c_2 in the fluid contained inside the pores of the stationary phase particles, and the concentration q_2 on the surfaces of the pores (solid-side) referred to the unit volume of particle. Because adsorption and desorption are assumed to be instantaneous, c_2 and q_2 are in equilibrium, so that only one of them is independent. Here, the equilibrium equation relating them, known as adsorption isotherm, is assumed to be linear; thus, we write $q_2 = ac_2$, where a is known as Henry coefficient. Finally, the analyte concentrations are assumed to depend solely on the spatial coordinate x along the axis of the chromatography column and on the time t.

2.1. The POR model

For each analyte, the concentrations in the mobile and stationary phases are governed by differential balance equations expressing the principle of mass conservation. Because c_2 and q_2 are functionally related, only two differential equations are necessary. In an infinitesimal slice of the column, the analyte can accumulate in the mobile phase, in the fluid within the pores, and on the surfaces of the pores; hence, three accumulations terms are present. Therefore, the accumulation rate per unit volume reads:

$$\epsilon_e \partial_t c_1 + (1-\epsilon_e)\epsilon_i \partial_t c_2 + (1-\epsilon_e)(1-\epsilon_i)\partial_t q_2$$
$$= \epsilon_e \partial_t c_1 + (1-\epsilon_e)\left[\epsilon_i + (1-\epsilon_i)a\right]\partial_t c_2$$
$$= \epsilon_e \partial_t c_1 + \epsilon_e\left[\left(\frac{1-\epsilon_e}{\epsilon_e}\right)\frac{\epsilon_i + (1-\epsilon_i)a}{a}\right]\partial_t q_2 = \epsilon_e(\partial_t c_1 + G\partial_t q_2) \quad (2.1)$$

with:

$$G \equiv \left(\frac{1-\epsilon_e}{\epsilon_e}\right)\frac{\epsilon_i + (1-\epsilon_i)a}{a} \quad (2.2)$$

and where ϵ_e and ϵ_i are the external and internal porosities [11], respectively. The analyte can enter and leave the infinitesimal slice of the column only via convection and (purely fluid dynamic) axial dispersion, so the mass balance equation reads:

$$\partial_t c_1(x,t) + G\partial_t q_2(x,t) = -U_x \partial_x c_1(x,t) + \mathscr{D}_x \partial_{xx}^2 c_1(x,t) \quad (2.3)$$

where we have divided throughout by ϵ_e, because this term appears in all the terms featuring in the equation. Above, U_x is the interstitial velocity (that is, the velocity at which a nonpenetrating nonretained tracer moves along the column) and $\mathscr{D}_x$ is the fluid dynamic dispersion coefficient.

The second differential equation can be written over a control volume coinciding with a stationary phase particle (assumed to be spherical). Here, the analyte mass varies only owing to mass transfer between the two phases, so the equation reads:

$$[\epsilon_i + (1-\epsilon_i)a]\partial_t c_2(x,t) = \frac{3k_e}{R}[c_1(x,t) - c_2(x,t)] \quad (2.4)$$

where k_e is the effective mass transfer coefficient that lumps the internal (inside the particle) and external (in the boundary layer around the particle) mass transfer resistances and R is the particle radius. On the right of the equation, $3/R$ expresses the specific external surface area

of the particle. Eq. (2.4) may be expressed more conveniently in terms of the concentration q_2 as follows:

$$\partial_t q_2(x,t) = \zeta [ac_1(x,t) - q_2(x,t)] \quad ; \quad \zeta \equiv \left[\frac{1}{\epsilon_i + (1-\epsilon_i)a}\right]\frac{3k_e}{R} \tag{2.5}$$

Eqs. (2.3) and (2.5) agree with equivalent equations reported in the literature; for instance, refer to Glueckauf & Coates [35] and Schmidt-Traub et al. [9] (in this reference, the authors refer to this model as transport dispersion model). Expressions for calculating $\mathscr{D}_x$ and k_e are also found in the literature [11,14,15,36].

2.2. The EDM model

In addition to the assumptions used in the POR model, the EDM also assumes that locally, along the column, the analyte concentrations in the mobile and stationary phases are in equilibrium, so that $c_1 = c_2 = q_2/a$. As a consequence, Eq. (2.5) is no longer needed. To account for the finite rate of mass transfer between the mobile and stationary phases, the model replaces $\mathscr{D}_x$ (i.e., the *fluid dynamic* dispersion coefficient) with an *apparent* dispersion coefficient [9,11].

In the literature, the EDM is sometimes written in terms of interstitial fluid velocity and some other times in terms of hypothetical fluid velocity (the velocity at which a penetrating nonretained tracer moves along the column). In the first case, the EDM differential mass balance equation is identical to Eq. (2.3), except that q_2 is eliminated with the equilibrium condition $q_2 = ac_1$ and $\mathscr{D}_x$ is replaced by an apparent dispersion coefficient, denoted here as $\mathscr{D}_a$. Accordingly, the equation reads:

$$(1 + aG)\partial_t c_1(x,t) = -U_x \partial_x c_1(x,t) + \mathscr{D}_a \partial_{xx}^2 c_1(x,t) \tag{2.6}$$

As reported in the literature [9], the hypothetical fluid velocity, denoted here as $\hat{U}_x$, is equal to the interstitial fluid velocity U_x times the term ϵ_e/ϵ_t, where $\epsilon_t \equiv \epsilon_e + (1-\epsilon_e)\epsilon_i$ denotes the total porosity in the column. Thus, to express Eq. (2.6) in terms of hypothetical fluid velocity, we must multiply the equation by ϵ_e/ϵ_t. This yields:

$$(\epsilon_e/\epsilon_t)(1 + aG)\partial_t c_1(x,t) = -\hat{U}_x \partial_x c_1(x,t) + (\epsilon_e/\epsilon_t)\mathscr{D}_a \partial_{xx}^2 c_1(x,t) \tag{2.7}$$

If we now define $\hat{\mathscr{D}}_a \equiv (\epsilon_e/\epsilon_t)\mathscr{D}_a$ and $F_t \equiv (1-\epsilon_t)/\epsilon_t$, and then use the relation $(1+aG)\epsilon_e = (1+aF_t)\epsilon_t$ (whose proof is left to the readers), we obtain:

$$(1 + aF_t)\partial_t c_1(x,t) = -\hat{U}_x \partial_x c_1(x,t) + \hat{\mathscr{D}}_a \partial_{xx}^2 c_1(x,t) \tag{2.8}$$

To use Eqs. (2.6) and (2.8), one requires an expression for the apparent dispersion coefficient. As mentioned, in the literature two are available. Opting for the formulation in terms of interstitial fluid velocity, Kostka et al. [19] suggested:

$$\mathscr{D}_a = \mathscr{D}_x + \frac{aGU_x^2}{\zeta(1+aG)^2} \tag{2.9}$$

Conversely, opting for the formulation in terms of hypothetical fluid velocity, Miyabe & Guiochon [10], as well as Guiochon et al. [11], suggested:

$$\hat{\mathscr{D}}_a = \mathscr{D}_x + \frac{aF_t\hat{U}_x^2}{\zeta(1+aF_t)^2} \tag{2.10}$$

These two expressions are not equivalent, and in fact they yield quite different predictions. As the reader can verify, the expression for $\hat{\mathscr{D}}_a$ equivalent to that given in Eq. (2.9) is:

$$\hat{\mathscr{D}}_a = \frac{\epsilon_e}{\epsilon_t}\left[\mathscr{D}_x + \frac{aGU_x^2}{\zeta(1+aG)^2}\right] = \frac{\epsilon_e}{\epsilon_t}\left[\mathscr{D}_x + \frac{aG\hat{U}_x^2}{\zeta(1+aF_t)^2}\right] \tag{2.11}$$

This relation coincides with that given in Eq. (2.10) only for $\epsilon_i = 0$, a condition that often is not fulfilled. This inconsistency motivated the main objective of this work: determining which expression is the correct one. To answer this question, we opted to derive the EDM from the POR

Table 1
Summary of the main equations of the POR model and of the EDM. In the EDM, the mass balances reduce from two to one. To compensate for the missing mass balance, the EDM replaces the fluid dynamic dispersion coefficient $\mathscr{D}_x$ with an apparent dispersion coefficient $\mathscr{D}_a$. The two reported versions of the EDM mass balance are equivalent, but the two closures for $\mathscr{D}_a$ are not.

Pore diffusion model – Mass balances

$$\partial_t c_1(x,t) + G\partial_t q_2(x,t) = -U_x \partial_x c_1(x,t) + \mathscr{D}_x \partial_{xx}^2 c_1(x,t)$$

$$\partial_t q_2(x,t) = \zeta[ac_1(x,t) - q_2(x,t)]$$

Equilibrium dispersion model – Mass balance
First formulation

$$(1 + aG)\partial_t c_1(x,t) = -U_x \partial_x c_1(x,t) + \mathscr{D}_a \partial_{xx}^2 c_1(x,t)$$

Second (equivalent) formulation

$$(1 + aF_t)\partial_t c_1(x,t) = -\hat{U}_x \partial_x c_1(x,t) + \hat{\mathscr{D}}_a \partial_{xx}^2 c_1(x,t)$$

Constitutive equations
First closure available in the literature

$$\mathscr{D}_a = \mathscr{D}_x + \frac{aGU_x^2}{\zeta(1+aG)^2} \quad \Rightarrow \quad \hat{\mathscr{D}}_a = \frac{\epsilon_e}{\epsilon_t}\left[\mathscr{D}_x + \frac{aG\hat{U}_x^2}{\zeta(1+aF_t)^2}\right]$$

Second (non-equivalent) closure available in the literature

$$\hat{\mathscr{D}}_a = \mathscr{D}_x + \frac{aF_t\hat{U}_x^2}{\zeta(1+aF_t)^2} \quad \Rightarrow \quad \mathscr{D}_a = \frac{\epsilon_e}{\epsilon_e}\left[\mathscr{D}_x + \frac{aF_t\hat{U}_x^2}{\zeta(1+aF_t)^2}\right]$$

Parameters

$$G \equiv \left(\frac{1-\epsilon_e}{\epsilon_e}\right)\frac{\epsilon_i + (1-\epsilon_i)a}{a} \quad ; \quad \zeta \equiv \left[\frac{1}{\epsilon_i + (1-\epsilon_i)a}\right]\frac{3k_e}{R}$$

$$F_t \equiv \frac{1-\epsilon_t}{\epsilon_t} \quad ; \quad \epsilon_t \equiv \epsilon_e + (1-\epsilon_e)\epsilon_i$$

model, using an asymptotic or perturbation method. For details about this powerful technique, we refer to the literature [34,37–39].

To help the readers to compare and contrast the POR model and the two versions of the EDM, we have summarized the main equations of these models in Table 1.

3. Derivation of the EDM via asymptotics

The starting point is the differential balance equations of the POR model, i.e., Eqs. (2.3) and (2.5). These feature various terms, each representing a physical process (e.g., axial dispersion) with a specific characteristic time. To obtain these times, we scale the variables (both dependent and independent) present in the equations. The scaled variables are:

$$\tau \equiv t/t_c \quad , \quad \bar{x} \equiv x/x_c \quad , \quad \bar{c}_1 \equiv c_1/c_{1,c} \quad , \quad \bar{q}_2 \equiv q_2/(ac_{1,c}) \tag{3.1}$$

The scalars at the denominators are the scales, which for now we leave unspecified. Because Eqs. (2.3) and (2.5) are linear, the value of $c_{1,c}$ is irrelevant; the scale of q_2 is equal to $ac_{1,c}$, because at equilibrium c_1 and q_2 must satisfy the linear adsorption isotherm. The scaled equations are:

$$\partial_\tau \bar{c}_1(\bar{x},\tau) + aG\partial_\tau \bar{q}_2(\bar{x},\tau) = -(U_x t_c/x_c)\partial_{\bar{x}}\bar{c}_1(\bar{x},\tau) + (\mathscr{D}_x t_c/x_c^2)\partial_{\bar{x}\bar{x}}^2 \bar{c}_1(\bar{x},\tau) \tag{3.2}$$

$$\partial_\tau \bar{q}_2(\bar{x},\tau) = (\zeta t_c)[\bar{c}_1(\bar{x},\tau) - \bar{q}_2(\bar{x},\tau)] \tag{3.3}$$

The characteristic times have now appeared: that of convection is x_c/U_x, that of dispersion is $x_c^2/\mathscr{D}_x$ and that of mass transfer is $1/\zeta$. We assume that mass transfer is very fast, convection is fast and dispersion is slow. In other words, we assume that:

$$\varepsilon \equiv U_x/\zeta x_c \ll 1 \quad ; \quad \text{Pe} \equiv U_x x_c/\mathscr{D}_x \gg 1 \tag{3.4}$$

Here, Pe is the Péclet number based on the length scale x_c (not on the length of the chromatography column). In Eq. (3.1), the time scale t_c must coincide with the characteristic time of the fastest process; hence, $t_c \equiv 1/\zeta$. Then, the nondimensionalized balance equations turn into:

$$\partial_\tau \bar{c}_1(\bar{x},\tau) + aG\partial_\tau \bar{q}_2(\bar{x},\tau) = -\varepsilon \partial_{\bar{x}} \bar{c}_1(\bar{x},\tau) + (\varepsilon/\text{Pe})\partial^2_{\bar{x}\bar{x}} \bar{c}_1(\bar{x},\tau) \tag{3.5}$$

$$\partial_\tau \bar{q}_2(\bar{x},\tau) = \bar{c}_1(\bar{x},\tau) - \bar{q}_2(\bar{x},\tau) \tag{3.6}$$

We know that $\varepsilon \ll 1$, and so we seek a solution in the form of a power series in this parameter. Following the method of perturbation theory, we write:

$$\bar{c}_1(\bar{x},\tau;\varepsilon) = \bar{c}_{1,0}(\bar{x},\tau) + \bar{c}_{1,1}(\bar{x},\tau)\varepsilon + O(\varepsilon^2) \tag{3.7}$$

$$\bar{q}_2(\bar{x},\tau;\varepsilon) = \bar{q}_{2,0}(\bar{x},\tau) + \bar{q}_{2,1}(\bar{x},\tau)\varepsilon + O(\varepsilon^2) \tag{3.8}$$

Let us briefly discuss the meaning of these equations; we refer to the first, but the same considerations apply also to the second. $\bar{c}_1$ is a function of $\bar{x}$ and τ (i.e., of the dimensionless space and time coordinates). But the mathematical problem features also various dimensionless numbers, e.g., a, Pe and ε, so $\bar{c}_1$ may be regarded as a function also of them. Hence, we can write $\bar{c}_1 = \bar{c}_1(\bar{x},\tau;a,\text{Pe},\varepsilon,\ldots)$. In our analysis, we want to fix the values of all the parameters except ε and investigate how the system behaves in the limit of vanishingly small values of ε (that is, in the limit of very fast mass transfer between the mobile and stationary phases). Thus, we lighten the notation and just write $\bar{c}_1 = \bar{c}_1(\bar{x},\tau;\varepsilon)$. We do not know this function (for we have not solved the mathematical problem), but we do know that the parameter ε is much smaller than unity. Thus, if we expand $\bar{c}_1 = \bar{c}_1(\bar{x},\tau;\varepsilon)$ in a Taylor series with respect to ε, choosing as expansion point $\varepsilon = 0$, and then retain only the first few terms of the expansion, we expect that the error of approximation should be small. Eq. (3.7) is this expansion, with $\bar{c}_{1,0}(\bar{x},\tau) \equiv \bar{c}_1(\bar{x},\tau;\varepsilon = 0)$ and $\bar{c}_{1,1}(\bar{x},\tau) \equiv \partial_\varepsilon \bar{c}_1(\bar{x},\tau;\varepsilon = 0)$.

Now, if we substitute the series into Eqs. (3.5) and (3.6) and equate coefficients of equal powers of ε, we get a set of equations. The first, the equations at leading order, are:

$$\partial_\tau \bar{c}_{1,0}(\bar{x},\tau) = -aG\partial_\tau \bar{q}_{2,0}(\bar{x},\tau) \quad ; \quad \partial_\tau \bar{q}_{2,0}(\bar{x},\tau) = \bar{c}_{1,0}(\bar{x},\tau) - \bar{q}_{2,0}(\bar{x},\tau) \tag{3.9}$$

These equations simply say that over a dimensionless time of order one, $\bar{c}_{1,0}$ and $\bar{q}_{2,0}$ become equal. In terms of real time, this equilibration process (driven by mass transfer) occurs over a time of order $1/\zeta$. Before the two concentrations become equal, $\bar{c}_1 - \bar{q}_2$ becomes small enough to make the mass transfer process as fast as the convection process; from this moment onward, the time scale of the system becomes the convection time; so, in Eq. (3.1), $t_c \equiv x_c/U_x$. The time interval where mass transfer dominates is very narrow and is referred to as temporal boundary layer; outside it, in the outer region, convection is as important as mass transfer and the time scale coincides with the characteristic time of convection. With this time scale, the nondimensionalized balance equations become:

$$\partial_\tau \bar{c}_1(\bar{x},\tau) + aG\partial_\tau \bar{q}_2(\bar{x},\tau) = -\partial_{\bar{x}} \bar{c}_1(\bar{x},\tau) + (1/\text{Pe})\partial^2_{\bar{x}\bar{x}} \bar{c}_1(\bar{x},\tau) \tag{3.10}$$

$$\varepsilon \partial_\tau \bar{q}_2(\bar{x},\tau) = \bar{c}_1(\bar{x},\tau) - \bar{q}_2(\bar{x},\tau) \tag{3.11}$$

We now operate as before. We seek a solution in the form of a power series in ε. Using Eqs. (3.7) and (3.8), we find a set of equations. Those at leading order read:

$$\partial_\tau \bar{c}_{1,0}(\bar{x},\tau) + aG\partial_\tau \bar{q}_{2,0}(\bar{x},\tau) = -\partial_{\bar{x}} \bar{c}_{1,0}(\bar{x},\tau) + (1/\text{Pe})\partial^2_{\bar{x}\bar{x}} \bar{c}_{1,0}(\bar{x},\tau) \tag{3.12}$$

$$\bar{c}_{1,0}(\bar{x},\tau) = \bar{q}_{2,0}(\bar{x},\tau) \tag{3.13}$$

whence:

$$(1 + aG)\partial_\tau \bar{c}_{1,0}(\bar{x},\tau) = -\partial_{\bar{x}} \bar{c}_{1,0}(\bar{x},\tau) + (1/\text{Pe})\partial^2_{\bar{x}\bar{x}} \bar{c}_{1,0}(\bar{x},\tau) \tag{3.14}$$

or equivalently:

$$\partial_\tau \bar{c}_{1,0}(\bar{x},\tau) = -V_0\partial_{\bar{x}} \bar{c}_{1,0}(\bar{x},\tau) + \mathscr{D}_0\partial^2_{\bar{x}\bar{x}} \bar{c}_{1,0}(\bar{x},\tau) \tag{3.15}$$

with:

$$V_0 \equiv (1 + aG)^{-1} \quad ; \quad \mathscr{D}_0 \equiv V_0/\text{Pe} \tag{3.16}$$

We would employ Eq. (3.14) if mass transfer was infinitely fast; but we are assuming it is extremely fast, so we must consider higher-order terms. At $O(\varepsilon)$, the equations read:

$$\partial_\tau \bar{c}_{1,1}(\bar{x},\tau) + aG\partial_\tau \bar{q}_{2,1}(\bar{x},\tau) = -\partial_{\bar{x}} \bar{c}_{1,1}(\bar{x},\tau) + (1/\text{Pe})\partial^2_{\bar{x}\bar{x}} \bar{c}_{1,1}(\bar{x},\tau) \tag{3.17}$$

$$\partial_\tau \bar{c}_{1,0}(\bar{x},\tau) = \bar{c}_{1,1}(\bar{x},\tau) - \bar{q}_{2,1}(\bar{x},\tau) \tag{3.18}$$

In Eq. (3.18), the term on the left is the time derivative of the *leading-order* concentration, given by Eq. (3.15). Thus, we can write Eq. (3.18) as follows:

$$\bar{q}_{2,1}(\bar{x},\tau) = \bar{c}_{1,1}(\bar{x},\tau) + V_0\partial_{\bar{x}} \bar{c}_{1,0}(\bar{x},\tau) - \mathscr{D}_0\partial^2_{\bar{x}\bar{x}} \bar{c}_{1,0}(\bar{x},\tau) \tag{3.19}$$

We now use this equation to eliminate $\bar{q}_{2,1}$ from Eq. (3.17), so that the latter features $\bar{c}_{1,1}$ only (then, Eq. (3.17) is no longer coupled with Eq. (3.18)). Doing so yields:

$$(1 + aG)\partial_\tau \bar{c}_{1,1}(\bar{x},\tau) = -\partial_{\bar{x}} \bar{c}_{1,1}(\bar{x},\tau) + (1/\text{Pe})\partial^2_{\bar{x}\bar{x}} \bar{c}_{1,1}(\bar{x},\tau)$$
$$- aG\partial_\tau \left[V_0\partial_{\bar{x}} \bar{c}_{1,0}(\bar{x},\tau) - \mathscr{D}_0\partial^2_{\bar{x}\bar{x}} \bar{c}_{1,0}(\bar{x},\tau) \right] \tag{3.20}$$

Now, we multiply all the terms in the equation above by ε, and then we sum the equation to Eq. (3.14). Because Eq. (3.7) holds, we obtain:

$$(1 + aG)\partial_\tau \bar{c}_1(\bar{x},\tau) = -\partial_{\bar{x}} \bar{c}_1(\bar{x},\tau) + (1/\text{Pe})\partial^2_{\bar{x}\bar{x}} \bar{c}_1(\bar{x},\tau)$$
$$- \varepsilon aG\partial_\tau \left[V_0\partial_{\bar{x}} \bar{c}_{1,0}(\bar{x},\tau) - \mathscr{D}_0\partial^2_{\bar{x}\bar{x}} \bar{c}_{1,0}(\bar{x},\tau) \right] + O(\varepsilon^2) \tag{3.21}$$

Now, we write:

$$\partial_\tau \left[V_0\partial_{\bar{x}} \bar{c}_{1,0}(\bar{x},\tau) - \mathscr{D}_0\partial^2_{\bar{x}\bar{x}} \bar{c}_{1,0}(\bar{x},\tau) \right] = \partial_{\bar{x}} \left[V_0\partial_\tau \bar{c}_{1,0}(\bar{x},\tau) - \mathscr{D}_0\partial^2_{\bar{x}\tau} \bar{c}_{1,0}(\bar{x},\tau) \right] \tag{3.22}$$

Then, using Eq. (3.15), we obtain:

$$\partial_\tau \left[V_0\partial_{\bar{x}} \bar{c}_{1,0}(\bar{x},\tau) - \mathscr{D}_0\partial^2_{\bar{x}\bar{x}} \bar{c}_{1,0}(\bar{x},\tau) \right] = -V_0\partial_{\bar{x}} \left[V_0\partial_{\bar{x}} \bar{c}_{1,0}(\bar{x},\tau) - \mathscr{D}_0\partial^2_{\bar{x}\bar{x}} \bar{c}_{1,0}(\bar{x},\tau) \right]$$
$$+ \mathscr{D}_0\partial^2_{\bar{x}\bar{x}} \left[V_0\partial_{\bar{x}} \bar{c}_{1,0}(\bar{x},\tau) - \mathscr{D}_0\partial^2_{\bar{x}\bar{x}} \bar{c}_{1,0}(\bar{x},\tau) \right] \tag{3.23}$$

This features four terms, whose orders of magnitude are very different; the first does not involve Pe, while the other three, when combined, are of order 1/Pe. Thus, we have:

$$\partial_\tau \left[V_0\partial_{\bar{x}} \bar{c}_{1,0}(\bar{x},\tau) - \mathscr{D}_0\partial^2_{\bar{x}\bar{x}} \bar{c}_{1,0}(\bar{x},\tau) \right] = -V_0^2\partial^2_{\bar{x}\bar{x}} \bar{c}_{1,0}(\bar{x},\tau) + O(1/\text{Pe}) \tag{3.24}$$

Eq. (3.20) now becomes:

$$(1 + aG)\partial_\tau \bar{c}_1(\bar{x},\tau) = -\partial_{\bar{x}} \bar{c}_1(\bar{x},\tau)$$
$$+ (1/\text{Pe})\partial^2_{\bar{x}\bar{x}} \bar{c}_1(\bar{x},\tau) + \varepsilon aGV_0^2\partial^2_{\bar{x}\bar{x}} \bar{c}_1(\bar{x},\tau) + O(\varepsilon/\text{Pe}) + O(\varepsilon^2) \tag{3.25}$$

Note that, in the term featuring V_0^2, we have replaced $\bar{c}_{1,0}$ with $\bar{c}_1$. Doing this is allowed at the approximation order at which we are working. In the equation above, the last two terms on the right-hand side are extremely small compared to the others (refer to Eq. (3.4)). Thus, these terms can be safely neglected. If we now go back to dimensional form, Eq. (3.25) turns into Eq. (2.6) with $\mathscr{D}_a$ given by Eq. (2.9).

This analysis has shown that the EDM can be rigorously derived from the more general POR model; the former may be regarded as the asymptotic approximation of the latter in the limit of very rapid mass transfer between mobile and stationary phases. The analysis has also given the analytical expression for the apparent dispersion coefficient, showing that between Eqs. (2.9) and (2.10), the former should be favoured. Finally, it has provided the conditions under which the EDM is valid, given by Eq. (3.4). In that equation, the length scale x_c should represent the average width of the analyte concentration spatial profile between the inlet and the outlet of the chromatography column. This can be easily estimated. Because the analyte moves along the column at velocity $U_x/(1 + aG)$, its residence time in the column is $(1 + aG)L/U_x$, where L is the column length. We know that over a given time t the order of magnitude of the spread induced by dispersion is $2\sqrt{\mathscr{D}t}$, where

$\mathscr{D}$ is the dispersion coefficient [37]. Therefore, if we assume that at the inlet of the column the concentration profile is very sharp (so that its width is negligible), considering that for the analyte in question the dispersion coefficient is equal to $\mathscr{D}_a/(1 + aG)$, we obtain $x_c \sim 2\sqrt{\mathscr{D}_a L/U_x}$. If the concentration profile at the inlet of the column is not very sharp, this estimate is invalid, but the correct one may be easily obtained with similar considerations.

To conclude this section, we would like to discuss why our expression for $\mathscr{D}_a$ differs from that of Miyabe & Guiochon [10] and Guiochon et al. [11]. To see why this happens, we must focus on the accumulation terms in Eq. (2.3). While we wrote it as $\partial_t c_1 + G\partial_t q_2$, Miyabe & Guiochon wrote it as $\partial_t c_1 + F_t \partial_t q_2$. The latter expression appears to be incorrect. As we discussed in Section 2.1, the analyte accumulates in three regions: in the mobile phase, in the fluid within the pores, and on the surfaces of the pores, so the accumulation terms should be three, not two. But both our model and that of Miyabe & Guiochon feature only two terms. To see why, let's write the expressions of the three terms; these are $\epsilon_e \partial_t c_1$, $(1 - \epsilon_e)\epsilon_i \partial_t c_2$, and $(1 - \epsilon_e)(1 - \epsilon_i)\partial_t q_2$, respectively. We assumed that c_2 and q_2 are in equilibrium – which implies assuming that the adsorption and desorption processes are infinitely fast. This permits combining the second and third accumulation terms, as shown in Eq. (2.1), leading to $\epsilon_e(\partial_t c_1 + G\partial_t q_2)$ as total accumulation term. Eq. (2.3) does not feature ϵ_e, for we divided by it throughout. Note that in the POR model we cannot assume c_1 and c_2, or equivalently ac_1 and q_2, to be equal, since the mass transfer between stationary and mobile phases is not assumed to be infinitely fast; this is shown by Eq. (2.5), which Miyabe & Guiochon also employ. However, this is precisely the assumption required to obtain the other expression for the total accumulation term. If we assume – *incorrectly* – that the concentrations c_1 and c_2 are equal, we can write:

$$\epsilon_e \partial_t c_1 + (1 - \epsilon_e)\epsilon_i \partial_t c_2 + (1 - \epsilon_e)(1 - \epsilon_i)\partial_t q_2$$
$$= \left[\epsilon_e + (1 - \epsilon_e)\epsilon_i\right]\partial_t c_1 + (1 - \epsilon_e)(1 - \epsilon_i)\partial_t q_2$$
$$= \epsilon_t \partial_t c_1 + (1 - \epsilon_t)\partial_t q_2 = \epsilon_t \partial_t c_1 + \epsilon_t\left(\frac{1 - \epsilon_t}{\epsilon_t}\right)\partial_t q_2 = \epsilon_t(\partial_t c_1 + F_t \partial_t q_2) \quad (3.26)$$

Then, dividing the entire differential mass balance equation (written in terms of hypothetical fluid velocity) by ϵ_t, we obtain the accumulation term of Miyabe & Guiochon. Hence, the differential equations that these authors use in the POR model are:

$$\partial_t c_1(x,t) + F_t \partial_t q_2(x,t) = -\hat{U}_x \partial_x c_1(x,t) + \hat{\mathscr{D}}_x \partial_{xx}^2 c_1(x,t) \quad (3.27)$$

$$\partial_t q_2(x,t) = \zeta[ac_1(x,t) - q_2(x,t)] \quad (3.28)$$

with $\hat{\mathscr{D}}_x \equiv (\epsilon_e/\epsilon_t)\mathscr{D}_x$. Applying the perturbation method to this set of equations, after similar mathematical passages, we obtain Eq. (2.8) with $\hat{\mathscr{D}}_a$ given by Eq. (2.10). This equation should not be used, because it is based on the incorrect assumption that ac_1 and q_2 are equal, a condition that in the POR model is not satisfied, as Eq. (3.28) clearly reveals. Eqs. (3.27) and (3.28) are incompatible.

It is encouraging to see that other authors have supported the correctness of Eq. (2.9). In particular, Qamar et al. [33] have derived this equation using the moment method analysis. In their work, they *postulated* the validity of the EDM model given by Eq. (2.6) and derived Eq. (2.9) by matching the analytical expressions of the second central moments of the analyte concentration profiles found from the analytical solutions of the EDM and GRM models. By *deriving* both Eqs. (2.6) and (2.9) from a more general chromatography model, our work offers a stronger theoretical grounding to these equations. Furthermore, as mentioned, it also provides clear applicability conditions for the model (Eq. (3.4)), which researchers and practitioners can use to verify that the EDM is valid for their specific systems of interest.

4. Numerical validation

To support our claim that Eq. (2.9) should be favoured when simulating chromatographic separations with the EDM, we simulated the

Table 2
Process parameters used in the EDM numerical simulations.

Symbol	Property	Value	Units
ϵ_t	Total porosity	0.55	–
ϵ_e	External porosity	0.25	–
L	Column length	0.15	m
D	Column diameter	$4.6 \cdot 10^{-3}$	m
R	Particle radius	$2.5 \cdot 10^{-6}$	m
k_e	Mass transfer coefficient	$3.2 \cdot 10^{-5}$	m/s
$\mathscr{D}_x$	Axial dispersion coefficient	$2.8 \cdot 10^{-8}$	m^2/s
a	Henry coefficient	5.69	–
Q	Volume flow rate	$1.7 \cdot 10^{-8}$	m^3/s
c_{IN}	Inlet concentration	0.50	kg/m^3
V	Sample volume	$5.0 \cdot 10^{-9}$	m^3

elution of a generic analyte employing both expressions for the apparent dispersion coefficient; that is, we used Eq. (2.6) coupled with:

$$\mathscr{D}_{a,1} = \mathscr{D}_x + \frac{aGU_x^2}{\zeta(1 + aG)^2} \quad \text{and} \quad \mathscr{D}_{a,2} = \frac{\epsilon_t}{\epsilon_e}\left[\mathscr{D}_x + \frac{aF_t\hat{U}_x^2}{\zeta(1 + aF_t)^2}\right] \quad (4.1)$$

We also simulated the system using the POR model, aiming to compare the results of the two versions of the EDM against those of the POR model (regarded as benchmark). Provided the EDM applicability conditions, given by Eq. (3.4), are met, the correct version of the EDM should yield results nearly identical to those of the POR model. We chose the process parameter values to satisfy this requirement; they are reported in Table 2. Since the inlet concentration profile was taken very sharp, the length scale x_c in Eq. (3.4) can be estimated with the relation $x_c \sim 2\sqrt{\mathscr{D}_a L/U_x}$. This yields 5 mm, whence $\epsilon = 8 \cdot 10^{-2}$ and Pe = 669; thus, the applicability conditions are satisfied.

To solve the three models, at the inlet and outlet of the chromatography column, we used the Danckwerts boundary conditions [11], given by:

$$c_1(x = 0, t) - (\mathscr{D}_a/U_x)\partial_x c_1(x = 0, t) = c_{IN} \quad ; \quad \partial_x c_1(x = L, t) = 0 \quad (4.2)$$

Here, c_{IN} is the analyte concentration at the inlet, but upstream, of the column. The boundary condition at the outlet of the column is adopted very frequently in chromatography – but its validity is not obvious. One may argue that as the analyte leaves the column, crossing its outlet section, $\partial_x c_1(x = L, t)$ cannot be zero, since the analyte concentration is not uniform (it has a bell shape). Therefore, it may seem that the outlet boundary condition given above should be rejected. However, in certain conditions, it is correct. Moreover, even when it is incorrect, one can prove that when Pe is far larger than unity (a requirement for the validity of the EDM and a condition that is often satisfied), that boundary condition can be adopted without affecting the accuracy of the results. For details, we refer to the Appendix.

The simulations were performed using gPROMS® ModelBuilder, discretizing the spatial grid (formed of 2000 elements) using the second-order Centred Finite Difference Method. The results of the simulations are shown in Fig. 1, which reports the analyte concentration at the outlet of the column as a function of time. As we can observe, the profiles obtained from the POR model and from the EDM coupled with the expression of $\mathscr{D}_{a,1}$ reported in Eq. (4.1) are nearly indistinguishable, whereas that based on the expression of $\mathscr{D}_{a,2}$ reported in Eq. (4.1) differs considerably from the other two.

5. Conclusions

The EDM is frequently used for designing and optimizing chromatographic processes. It is convenient, since it involves only one differential mass balance equation per analyte. This is possible since the model assumes that the analyte concentrations in the mobile and stationary phases are in equilibrium, a condition that would require an infinite mass transfer rate between the two phases. Because the real mass transfer rate is finite, the model replaces the fluid dynamic dis-
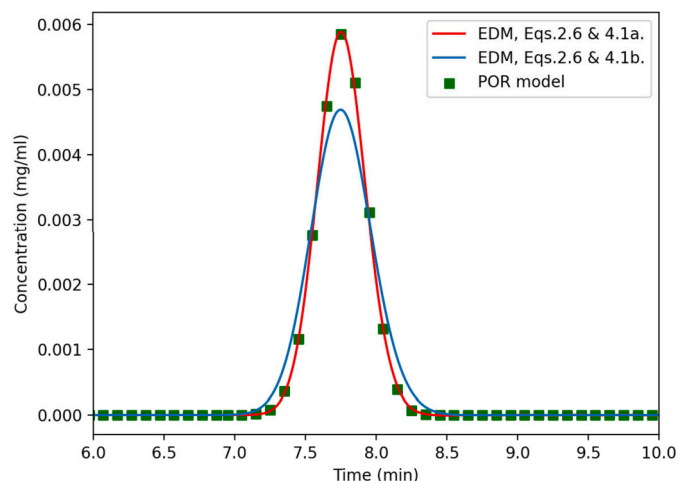
Fig. 1. Comparison between the simulated profiles of the POR model and of the two versions of the EDM obtained by coupling Eq. (2.6) with the two apparent dispersion coefficients given in Eq. (4.1).

persion coefficient present in the analyte mass balance equation with an apparent one, related to fluid dynamics, mass transfer and thermodynamics (adsorption isotherm). Finding a suitable expression for this dispersion coefficient is a critical part of this modeling strategy. In the literature, two expressions are available, their predictions differing significantly. In this work, we intended to determine which expression should be favoured. To do this, we derived the EDM from the more general POR model via an asymptotic method; this technique provides a stronger foundation for the EDM model, gives an analytical expression for the apparent dispersion coefficient and specifies the applicability conditions of the model. The expression that we obtained does coincide with one of those available in the literature, but this appears to be the less frequently adopted. To confirm the validity of our analysis, we simulated a chromatographic process using the POR model and the two versions of the EDM, selecting conditions that meet the EDM applicability criteria provided by the asymptotic analysis. In such conditions, the POR and the correct version of the EDM should yield almost identical results. This is indeed what we observed, the simulation results confirming that the expression for the apparent dispersion coefficient supported by our analysis should be favoured.

CRediT authorship contribution statement

Konstantinos Katsoulas: Data curation, Investigation, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Monica Tirapelle:** Data curation, Investigation, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Eva Sorensen:** Funding acquisition, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. **Luca Mazzei:** Conceptualization, Formal analysis, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The authors declare that financial support was provided by the Engineering and Physical Sciences Research Council (EPSRC), grant code EP/T005556/1.

Data availability

Data will be made available on request.

Appendix A

A.1. On the EDM outlet boundary condition

Let us consider a chromatographic system which consists of three parts: an inlet section, the chromatography column, and an outlet section. At the boundaries between them (located at $x = 0$ and $x = L$, that is, at the inlet and outlet of the column), one assumes that both the concentration and the mass flow rate of the analyte are continuous [40]. Thus, at the column outlet, it is:

$$S \epsilon_e (U_x c_1 - \mathscr{D}_a \partial_x c_1) = S_o \epsilon_{e,o} (U_{x,o} c_1 - \mathscr{D}_{x,o} \partial_x c_{1,o}) \qquad \text{(A.1)}$$

where S denotes the area of the cross-section of the column, and the symbols with the subscript o refer to the outlet section of the system. It is understood that all the variables are evaluated at $x = L$. Moreover, on the right-hand side of Eq. (A.1), using the assumption that the concentration is continuous, we have replaced $c_{1,o}$ with c_1. Notice that the outlet section involves not the apparent dispersion coefficient but the fluid dynamic one. If we assume that the fluid is incompressible, then mass conservation requires that $S \epsilon_e U_x = S_o \epsilon_{e,o} U_{x,o}$. Therefore, Eq. (A.1) reduces to:

$$\partial_x c_1 = (U_x \mathscr{D}_{x,o} / U_{x,o} \mathscr{D}_a) \partial_x c_{1,o} \qquad \text{(A.2)}$$

Often, in the literature it is assumed that in the outlet section fluid dynamic dispersion is negligibly small. If in Eq. (A.2) we make $\mathscr{D}_{x,o}$ *tend* to zero, then, *provided that* $\partial_x c_{1,o}$ *remains finite* (as we shall presently see, this is indeed the case), the equation yields $\partial_x c_1 = 0$. This is the outlet boundary condition in Eq. (4.2), which was first advanced by Danckwerts [41] during the study of steady-state reactors. For chromatography columns, this condition might surprise: when an analyte leaves the column, its concentration is not uniform (it usually has a bell shape), so how can its spatial derivative vanish? Moreover, when the function $c_1(x, t)$ is plotted, in most cases near the outlet of the column one does not see a region where the concentration gradient gradually reduces to eventually vanish at the outlet. So, at $x = L$, does $\partial_x c_1$ really go to zero? Before answering these questions, we point out that if in the outlet section fluid dynamic dispersion is not negligible, Eq. (A.2) must be used. This is inconvenient, because it implies that also the outlet section must be modeled [40]. Fortunately, in most chromatographic systems, convection dominates over dispersion. As we shall see, when this happens, one can still adopt the condition $\partial_x c_1 = 0$, without altering the solution in most of the column. But understanding the reason for this is important.

Consider Eq. (2.6), i.e., the differential equation characterizing the EDM. As this involves a second-order derivative with respect to x, the model requires two boundary conditions. The right-hand side of the equation features a convection and a dispersion term, whose relative importance one can judge by scaling the equation [37,42,43]. Doing this leads to Eq. (3.10). In a correctly scaled equation, the dimensionless derivatives have unit order of magnitude; hence, the relative importance of the various terms is revealed by the factors by which the derivatives are multiplied [37]. In Eq. (3.10), such factors are 1 for the convection term and $1/\text{Pe}$ for the dispersion term. Consequently, if $\text{Pe} \gg 1$, we conclude that the dispersion term is very small compared with the convection term. In light of this, one may rightly eliminate it (at the lowest order of approximation), solving the simplified differential equation:

$$(1 + aG) \partial_t c_1(x, t) = -U_x \partial_x c_1(x, t) \qquad \text{(A.3)}$$

But this equation features only a first-order derivative with respect to x, and thus requires only one boundary condition. When this situation arises, a *boundary layer* – in our case, a concentration boundary layer – exists near one of the two boundaries [34,37]. In the problem at hand, *the boundary layer is located at the outlet of the column*; here, the analyte concentration changes significantly not over the length x_c introduced in Section 3 but over a far shorter length (the boundary layer thickness), so that no matter how large Pe is, in the boundary layer the dispersion term is not negligible and the outlet boundary condition is not lost. *The outlet boundary condition influences the solution solely within the boundary layer*; in the rest of the domain (referred to as the outer region), the solution is virtually unaffected by the outlet boundary condition. In several applications, this overcomes the issue of assigning the outlet boundary condition – a very fortunate outcome, insofar as often this condition is unknown [44].

In our case, if in the outlet section fluid dynamic dispersion is negligible, the outlet boundary condition is known, being $\partial_x c_1 = 0$. As just said, this condition affects the concentration profile only extremely near the column outlet; outside this thin region, the profile has the expected bell shape. This also explains why when we plot the variable c_1 against x, we usually do not see a region where the concentration gradient gradually reduces to eventually vanish at the column outlet; we do not see it, because this region is extremely thin. But if a sufficiently fine computational grid is used, zooming in close to the column outlet will reveal this region. If in the outlet section fluid dynamic dispersion is not negligible, we can still adopt the (incorrect) condition $\partial_x c_1 = 0$, but we must disregard the part of the solution that falls within the boundary layer, considering as column outlet concentration the value of $c_1(x, t)$ immediately upstream of the boundary layer. This location can be easily estimated. The boundary layer must be thin enough to permit the dispersion term to balance the convection term; the latter scales as U_x/δ, where δ is the boundary layer thickness, while the former scales as $\mathscr{D}_a/\delta^2$. To balance, these terms must have the same order of magnitude; that is, $U_x/\delta \sim \mathscr{D}_a/\delta^2$. From this condition, we obtain $\delta/L \sim \mathscr{D}_a/U_x L$ or equivalently $\delta/L \sim 1/\mathrm{Pe}_L$, where Pe_L is a Péclet number based on the length of the chromatography column and on the apparent dispersion coefficient. Hence, the location just upstream of the outlet boundary layer is at $x_L \sim (1 - 1/\mathrm{Pe}_L)L$.

A final remark about the condition $\partial_x c_1 = 0$ is in order. We obtained this condition by taking the limit of Eq. (A.2) for $\mathscr{D}_{x,o} \to 0$, in the assumption that as $\mathscr{D}_{x,o}$ goes to zero, $\partial_x c_{1,o}$ remains finite at $x = L$. When $\mathscr{D}_{x,o}$ goes to zero, also in the outlet section a concentration boundary layer arises, its thickness being proportional to $\mathscr{D}_{x,o}$. Hence, for $\mathscr{D}_{x,o} \to 0$, $\partial_x c_{1,o}$ tends to diverge in the boundary layer (because the gradient is inversely proportional to the boundary layer thickness). But the boundary layer lies *at the end* of the outlet section, not at $x = L$. Consequently, $\partial_x c_{1,o}$ remains finite at $x = L$. Note that the same is not true for the inlet section of the chromatographic system; here, when the dispersion coefficient $\mathscr{D}_{x,i}$ goes to zero, a boundary layer forms at $x = 0$ (that is, *at the end* of the inlet section), and so the concentration gradient $\partial_x c_{1,i}$ diverges at $x = 0$, creating a discontinuity in the concentration profile; this is present in the inlet boundary condition reported in Eq. (4.2), where $c_1(x = 0, t) \neq c_{IN}$. Of course, this discontinuity will never occur in reality, because in a real system the dispersion coefficient will never be zero.

To confirm the validity of these considerations, we solved Eq. (2.6), with the first relation for the apparent dispersion coefficient reported in Eq. (4.1), using these outlet boundary conditions:

$$\partial_x c_1(x = L, t) = 0 \, \mathrm{kg/m^4} \quad ; \quad \partial_x c_1(x = L, t) = 5 \, \mathrm{kg/m^4} \quad ;$$

$$\partial_x c_1(x = L, t) = 10 \, \mathrm{kg/m^4} \tag{A.4}$$

Fig. 2 shows the analyte concentration spatial profiles at a time ($t = 4$ m) where the profiles are far from the column outlet; as we can see, the outlet boundary condition does not affect the solution: the three profiles are identical. This is true at any spatial location that lies outside
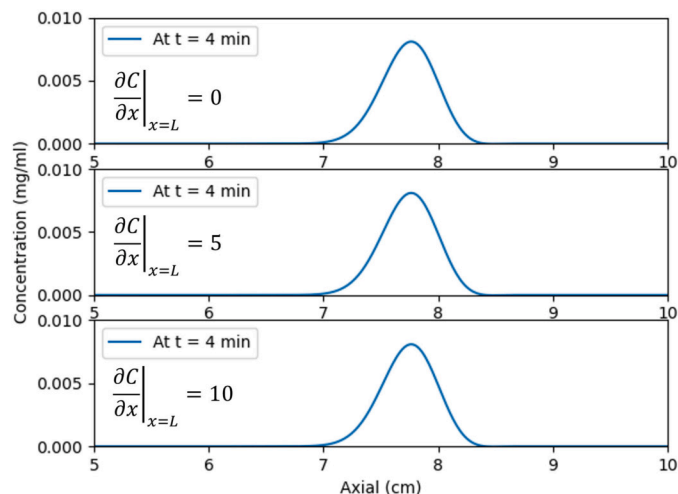

Fig. 2. Spatial concentration profiles far from the outlet of the column calculated with the outlet boundary conditions reported in Eq. (A.2).
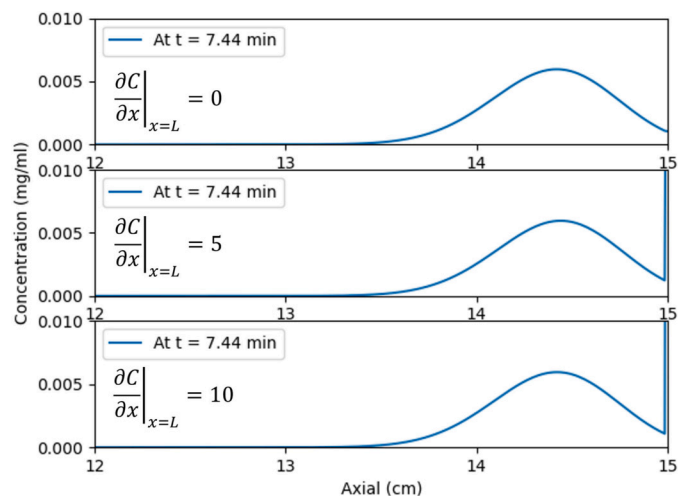

Fig. 3. Spatial concentration profiles close to the outlet of the column calculated with the outlet boundary conditions reported in Eq. (A.2).

the outlet boundary layer; i.e., for any $x < x_L$. Fig. 3 shows the analyte concentration spatial profiles at a time ($t \approx 7$ m) where the profiles are crossing the column outlet. As we can see, only the very final part of the profiles (the part lying within the outlet boundary layer) is affected by the outlet boundary condition, and while the boundary conditions that set $\partial_x c_1(x = L, t)$ different from zero create a sudden change in concentration, the condition that sets the concentration gradient to zero does preserve the value of the concentration immediately upstream of the outlet boundary layer. This confirms the validity of our previous considerations.

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