Plate Models in Chromatography: Analysis and Implications for Scale-Up

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Detailed chromatographic rate theories from the literature can be used to determine the appropriate plate count for a plate model of linear chromatography so that the headspreading generated by the detailed rate model is reproduced by the plate model. This process provides a link between the plate count and the physical parameters that cause headspreading. Each sample component can be assigned an appropriate plate count, thus allowing the accurate simulation of multicomponent separations even for widely differing adsorbates. Analytical solutions are presented for the Craig distribution and the continuous plate model for both finite-pulse elution and frontal chromatography. The Craig model is widely considered unsuitable because it assumes discontinuous flow; it is shown that, for a suitably corrected plate count, the Craig model is as accurate as the continuous-flow plate theory (except for the case of an unretained solvent). Direct calculation of effluent histories from these plate models show excellent agreement between themselves and with results from complex rate models available in the literature. Reasonable agreement is also found when the plate models are used a priori to predict experimental scale-up results.
List of Symbols

c  mobile phase concentration, M

$D_e$  effective micropore diffusivity, $m^2 s^{-1}$

$D_m$  effective macropore diffusivity, $m^2 s^{-1}$

$D_t$  effective axial dispersion coefficient, $m^2 s^{-1}$

$I_{i(a,b)}$  incomplete beta function, $= \int_a^b t^{i-1} (1 - t)^{b-i-1} dt$

$J$  plate count in continuous-flow plate model

$k_c$  external film mass transfer coefficient, $m s^{-1}$

$K^*$  dimensionless distribution coefficient; subscript i indicates i$^\text{th}$ component

$K'_s$  overall distribution coefficient, $= c_s + (1 - c_s)K^*_s$

$k'$  retention factor, dimensionless

$L$  column length, m

$M$  input pulse width (discretized)

$N$  number of spatial segments in the Craig simulation

$N_{\text{plate}}$  plate count

$p_i$  probability of i$^\text{th}$ species being in the mobile phase

$P(a,x)$  incomplete gamma function, $= \frac{\int_0^a x^{i-1} e^{-x} dx}{\int_0^\infty x^{i-1} e^{-x} dx}$

$P_{\text{mc}}$  microparticle Peclet number, $u(2r_p) D_t$, dimensionless

$P_{\text{p}}$  pellet Peclet number, $u(2r_p) D_t$, dimensionless

$P_{\text{be}}$  bed Peclet number, $uL/D_t$, dimensionless

$P_c$  equivalent Peclet number in the axial-dispersion model

$q_i$  stationary phase concentration, M

$q_i$  probability of i$^\text{th}$ species being bound to the stationary phase

$r_p$  microparticle radius, m

$r_s$  pellet radius, m

$Sh$  Sherwood number, $k_r(2r_p) D_t$, dimensionless

$t$  time, s

$t_a$  retention time (first moment), s

$\Delta t$  time increment in the Craig simulation, s

$v$  superficial velocity, $m s^{-1}$

$v$  mobile phase velocity, $m s^{-1}$

$v_m$  interstitial velocity, $m s^{-1}$

$x$  axial coordinate, m

$\Delta x$  axial space increment, m
Plates Models in Chromatography

Subscripts
F \quad \text{frontal chromatography}
\ i \quad \text{i}^\text{th} \ \text{component}
\ j \quad \text{j}^\text{th} \ \text{plate}
\ k \quad \text{k}^\text{th} \ \text{time interval}

Greek Symbols
\alpha \quad \text{coefficient in the continuous-flow plate solution}, \quad \frac{N_{ij}}{t_{k,i}}, \quad \text{s}^{-1}
\delta \quad \text{scaled microparticle radius}, \quad \frac{r_1}{L}, \quad \text{dimensionless}
\delta_s \quad \text{scale pellet radius}, \quad \frac{r_1}{L}, \quad \text{dimensionless}
\varepsilon \quad \text{micropore porosity, m}^3 \ \text{micropores per m}^3 \ \text{microparticles}
\varepsilon_r \quad \text{macropore porosity, m}^3 \ \text{macropores per m}^3 \ \text{pellet}
\epsilon_b \quad \text{bed porosity, m}^3 \ \text{bed voids per m}^3 \ \text{bed}
\phi \quad \text{volumetric phase ratio, dimensionless}
\mu^0 \quad \text{zeroth temporal moment, M s}
\mu_1 \quad \text{first temporal moment, s}
\mu_2 \quad \text{second temporal moment, s}^2
\beta_2 \quad \text{second central temporal moment, s}^2
\tau \quad \text{input pulse width, s}
1 Introduction

Analyses of linear chromatography are traditionally divided into two classes: the rate and the plate theories [1, 2]. The rate theories reflect the various mass-transfer and diffusion processes that occur in the chromatographic column in addition to sorption. The major advantage that these theories possess is their explicit dependence on the physical parameters involved in bandspeading, such as the film mass-transfer coefficient and the pore diffusivity. In contrast, the plate theories lump the various bandspeading contributions into a plate height that can conceptually be regarded as a measure of non-equilibrium. While this simplifies the mathematical treatment, the plate height is not directly related to the physical parameters that cause bandspeading, and these models are hence considered empirical [3].

It is possible to generate the equivalent of a plate height from the results of a rate model, and many such height-equivalent-to-a-theoretical-plate (HETP) expressions [1, 4–7] exist in the literature. Such HETP expressions have been used to examine how the bandspeading is affected by the column characteristics and operational variables, e.g., the van Deemter expression for HETP as a function of axial flow velocity [7].

General expressions for the effluent history are presented for both the Craig and the continuous-flow plate models for multicomponent linear frontal and elution chromatography. The drawback that is usually associated with the Craig model — that it substantially overestimates the resolution between peaks as well as the plate count — is shown to rest on an inappropriate definition of plate count. The Craig model can therefore be used wherever the continuous-flow plate model is applicable, except in the case of an unretracted component, for which it erroneously predicts zero bandspeading. The relation between Craig plates and plug flow reactor segments is brought out. The analytical expressions for effluent history lend themselves to scale-up: the design parameters such as particle diameter and column dimensions can be varied, the resulting plate number calculated, and the appropriate plate solution (which is explicitly known) used to examine the quality of the separation. Since each step in this process has an explicit analytical expression, optimization is facilitated.

2 Theory

2.1 Theoretical Determination of Plate Count

Numerous solutions express H (the HETP) and the corresponding plate count \( N_{\text{plate}} = L/H \), where \( L \) is the column length, as the sum of contributions from various physical processes [3, 6, 8, 9]. Here we use Haynes' results [10]. The first
moment (retention time) is given by

\begin{align*}
\mu_{1,i} &= \frac{L}{u} \left[ \varepsilon_u + (1 - \varepsilon_u) \varepsilon_r + (1 - \varepsilon_r)(1 - \varepsilon_r) \varepsilon_u (1 + K^4) \right] \\
&= \frac{L}{u} \left[ \varepsilon_u + (1 - \varepsilon_u) \varepsilon_r + (1 - \varepsilon_r)(1 - \varepsilon_r) \varepsilon_u + (1 - \varepsilon_r)(1 - \varepsilon_u) \varepsilon_r K^4 \right] \\
&= \frac{L}{u} \left[ 1 + \phi K^4 \right] \\
\end{align*}

where \( \nu = \frac{u}{\varepsilon_u + (1 - \varepsilon_u) \varepsilon_r + (1 - \varepsilon_r)(1 - \varepsilon_r) \varepsilon_u} \) \hspace{2cm} (2)

and \( \phi = \frac{(1 - \varepsilon_r)(1 - \varepsilon_u) \varepsilon_r}{\varepsilon_u + (1 - \varepsilon_u) \varepsilon_r + (1 - \varepsilon_r)(1 - \varepsilon_r) \varepsilon_u} \) \hspace{2cm} (3)

The volumetric phase ratio for the lumped models is defined by Eq. (3). Eq. (2) relates the mobile phase or chromatographic velocity, \( v \), to the superficial velocity, \( u \).

The plate count (defined as the ratio of the square of the first moment to the second central moment) is given by [10]

\begin{align*}
\frac{1}{N_{\text{plate}}} &= \frac{2}{P_{e_s}} \left[ \frac{(1 - \varepsilon_s) \beta^2}{3 \varepsilon_r + (1 - \varepsilon_r) \beta} \right] + \frac{2 P_{e_s} \delta_s}{15} \\
&= \frac{(1 - \varepsilon_s)(1 - \varepsilon_r)^2}{15 (1 - \varepsilon_s) \varepsilon_r + (1 - \varepsilon_r) \beta} \left( \frac{1}{P_{e_s} \delta_s} \right) \\
&= \frac{1}{P_{e_s} \delta_s} \left( \frac{2}{3 (1 - \varepsilon_s) \beta} + \frac{1}{15 (1 - \varepsilon_s) \varepsilon_r} + \frac{1}{15 (1 - \varepsilon_r) (1 - \varepsilon_s)} \right) \hspace{2cm} (4)
\end{align*}

where \( \beta = \varepsilon_s + (1 - \varepsilon_s) \varepsilon_r (1 + K^4) \) \hspace{2cm} (5)

and the usual dimensionless terms (see List of Symbols) have been introduced.

The plate count for each component can be calculated from Eq. (4) by substituting the appropriate dimensionless quantities; the component subscript is omitted for clarity.

When \((1 - \varepsilon_s) \beta \gg \varepsilon_r \) and \( \beta \gg \varepsilon_r \), which are true for strongly-retained compounds, Eq. (4) reduces to the more familiar form [11]:

\begin{align*}
\frac{1}{N_{\text{plate}}} &= \frac{2}{P_{e_s}} + \frac{2 P_{e_s} \delta_s}{3 (1 - \varepsilon_s) \beta} + \frac{1}{15 (1 - \varepsilon_s) \varepsilon_r} + \frac{1}{15 (1 - \varepsilon_r) (1 - \varepsilon_s)} \hspace{2cm} (6)
\end{align*}

It should be noted that Haynes and Sharma define their distribution coefficient, \( K^4 \), by

\begin{align*}
K^4 &= \frac{\rho S_s}{C_s (1 - \varepsilon_s) C_r} \hspace{2cm} (7)
\end{align*}

since their stationary phase concentration, \( C_s \), is expressed in \( \text{g mole cm}^{-2} \). Suitable modifications must be made if volumetric units are used instead. Further, Eq. (4) does not account for finite sorption rates, surface diffusion and bulk flow effects. If these contributions to bandspeading become significant in
a given separation, the appropriate result for the plate count [12, 13] can be
used in place of Eq. (4).

2.2 Craig Model

The Craig model is given by

$$c(i, j, k) + \phi q(i, j, k) = c(i, j - 1, k - 1) + \phi q(i, j, k - 1)$$

where $c(i, j, k)$ is the mobile phase concentration of the $i^{th}$ species in the $j^{th}$ plate
at the $k^{th}$ instant, $q(i, j, k)$ is the corresponding stationary phase concentration,
and $\phi$ is the phase ratio. Using $q = K^c$ and $k' = \phi K^s$, there follows

$$I + k')c(i, j, k) = c(i, j - 1, k - 1) + k'c(i, j, k - 1)$$

Eq. (9) is a linear partial difference equation, whose solution can be found using
standard methods [14, 15]. The analytical solutions to linear frontal chromatography
and linear elution chromatography (when the pulse input fills several plates) are derived by
the method of the two-dimensional $z$-transform in Appendix I, only the final forms are given here. The solution for linear elution is

$$c(i, j, k) = \frac{(p_0)^j}{c_0} \sum_{m=0}^{k-j} \binom{j + m - 1}{m} (q_0)^m, \hspace{1cm} k - j < M$$

where

$$p' = 1/(1 + k')$$

$$q' = k'/I(1 + k')$$

and $M$ is the input pulse width, and $\binom{n}{r}$ is the binomial coefficient.

The analogous solution for frontal chromatography is

$$c_0(i, j, k) = \frac{(p_0)^j}{c_0} \sum_{m=0}^{k-j} \binom{j + m - 1}{m} (q_0)^m$$

The effluent history (the experimentally obtained chromatogram) for a column
of $N_j$ plates is thus obtained by substituting $j = N_j$ in Eq. (10).

As is well known [16, 17], the Craig distribution results in a binomial
distribution for the peak profile on-column. Equations (10) and (11) simply
represent the finite sums of such binomial distributions, appropriate to inputs of
a pulse of finite width and a step, respectively.

The results in Eqs. (10) and (11) can be formally generalized to non-integral
$J$ (plate count) and $M$ (input pulse width) by making use of the identity

$$(p_0)^j \sum_{m=0}^{k-j} \binom{j + m - 1}{m} (q_0)^m = I_I(j, k - j)$$
where the right-hand-side of Eq. (12) is an incomplete beta function [18]. Thus the frontal solution can be represented as

\[ \frac{c_i(t, N_i, k)}{c_0} = I_p(N_i, k - N_i) \]

(13)

where \( p_i \) is the probability of the \( i \)th species being in the mobile phase. The corresponding result for elution is

\[ \frac{c_i(t, N_{e_i}, k)}{c_0} = I_p(N_i, k - N_i) - I_p(N_i, k - N_i - M) \]

(14)

Since the arguments of the incomplete beta function do not need to be integers, rational numbers may be used for \( N_i \) and \( M \) in Eqs. (13) and (14). Equation (12) is found in the theory of statistics [19]; an analogous result can be seen in the early work of Steine [20] on extraction.

The calculation of moments for the Craig distribution is also well established [21, 22]. These relations lead to a link between the plate count as defined earlier and the number of plates in the Craig column:

\[ N_{\text{plate, } i} = N_i \left( \frac{1 + k_i^2}{k_i} \right) \]

(15)

Using Eq. (4) to calculate \( N_{\text{plate, } i} \), the plate count of the \( i \)th component, and Eq. (15) allows the calculation of \( N_i \), the number of divisions in a Craig column for which the same band spreading will be produced. Setting \( j = N_i \) in Eqs. (10) or (11) gives the corresponding analytical expression for the chromatogram.

The restriction to linear chromatography (required by Eq. (4)) guarantees that each component traverses the column independently of all others. Consequently, a plate count \( N_{\text{plate, } i} \), can be determined for each component and the corresponding Craig plate number \( N_i \) determined. The analytical solutions for the multicomponent separation are then available without making the usual assumption that the components must be similar so that an average plate count can be used.

### 2.3 Continuous-Flow Plate Model

Also known as the "stirred-tank-in-series" model, this has also been widely used [17, 23–26]. The column is regarded as a series of vessels in each of which complete mixing and instantaneous equilibrium occurs. While the distance variable is thus discretized, time is retained as a continuous variable.

The mass balance within the \( j \)th vessel is

\[ V_r \frac{dc_i(j, t)}{dt} + V_r (1 - \varepsilon_r) \frac{dq(i, j, t)}{dt} = F [c(i, j - 1, t) - c(i, j, t)] \]

(16)

where \( V_r \) is the volume of the vessel, \( \varepsilon_r \) the total porosity (as in Eqs. (1)–(3), this could be a combination of various porosities when compared to a complex rate model), and \( F \) the volumetric flow rate. The concentration notation is an
extension of that previously used. As before this can be rewritten as

\[
(1 + k) \frac{dc(i, j, t)}{dt} = \frac{v}{(\Delta x)} [c(i, j - 1, t) - c(i, j, t)]
\]

\[
= \frac{1}{(\Delta x)} [c(i, j - 1, t) - c(i, j, t)]
\]  

(17)

where \( v \) is the mobile-phase velocity, \( \Delta x (= L/N) \) is the length of the plate, and
\( v = \Delta x / \Delta t \).

Using \( t_0 = L/v \) and \( t_k = t_0(1 + k') \), there follows

\[
\frac{dc(i, j, t)}{dt} = \frac{N_i}{t_k} [c(i, j - 1, t) - c(i, j, t)] \quad j = 1, 2, \ldots, N_i
\]

(18)

The solution to the system represented by Eq. (18) is well known [e.g., 17]. For frontal chromatography with \( J \) plates, the chromatographic effluent history is given by

\[
c_i(i, J, t) = 1 - e^{-a_i \sum_{j=0}^{J-1} (a_t)^j} = e^{-a_i \sum_{j=0}^{J-1} (a_t)^j} = e^{-a_i \sum_{j=0}^{J-1} (a_t)^j}
\]

(19)

where \( a_i = N_i / t_k \). The corresponding elution profile, when the injection time of the pulse is \( \tau \), is given by

\[
\frac{c_i(i, j, t)}{c_0} = e^{-a_i \sum_{j=0}^{J-1} (a_t)^j} = e^{-a_i \sum_{j=0}^{J-1} (a_t)^j}
\]

(20)

These analytical expressions are easy to use, and their moments (essentially those of the Poisson distribution) can be easily calculated [21]. Upon using these to evaluate the plate count, we get

\[
J_i = N_{\text{plate},i}
\]

(21)

This equality is to be expected because the usual definition of plate count, Eq. (20), is in fact derived from continuous-flow plate theory [17]. It may be noted that the absence of the retention factor, in Eq. (21), together with the nature of the dependence of \( N_{\text{plate},i} \) on \( k' \) as seen in Eq. (4) imply that the continuous plate model will successfully predict the retention of an unretained solute.

These results for integral \( J \) can again be formally generalized as was done earlier for the Craig simulation. For all real \( J \), the analog to Eq. (19) is

\[
c_i(i, J, t) = P\left(J, J_1 \frac{1}{t_k}ight)
\]

(22)

where the right-hand-side is one form of the incomplete gamma function [18]. Similarly, the result for elution is

\[
\frac{c_i(i, J, t)}{c_0} = P\left(J, J_1 \frac{1}{t_k}ight) - P\left(J, J_1 \left(1 - \frac{\tau}{t_k}\right)\right)
\]

(23)

An analogous result for extraction was again given by Steen [20].
2.4 Viability of the Craig Model

Ever since Glueckauf [24] stated in 1954 that the Craig, or discontinuous-flow, plate model as described by Mayer and Tompkins [27] overestimated the resolution achieved by a given column, its use has been limited. Glueckauf noted that the discrepancy is at all times quite significant but becomes extremely large for weakly-retained components: for example, the calculated number of theoretical plates is in error by over 100% for a component whose distribution coefficient is less than unity. However, we shall show below that when the plate count for the Craig model is appropriately defined, the Craig and continuous-flow plate models give very similar results. The only exception is an unretained component, for which, as is well known, the Craig model would give no bandspeading, i.e., the shape of the band is not altered at all by passage through the chromatographic column. This is obviously incorrect, since unretained components will also spread as a result of such processes as axial dispersion and pore diffusion, but this case is of limited practical interest.

First, we apply the results derived above to the case of frontal chromatography of one component through a single plate. This is obviously an unrealistic process, but serves to contrast the behavior of the two plate models, and can be generalized.

From Eq. (11), the effluent history for the Craig model is given by

$$\frac{c_{j+1}(k)}{c_0} = p^j \sum_{m=0}^{k-1} (q)^m$$

(24)

where the subscript i has been dropped, since only one component is being considered, and j = 1 (exactly one plate). This expression involves the sum of a geometric series; when this is evaluated, the result is

$$\frac{c_j^{(1)}(k)}{c_0} = 1 - (q')^k = 1 - (1 - p')^k$$

(25)

The superscript "disc" standing for "discrete flow" or "discontinuous flow," has been added to distinguish the Craig from the continuous-flow model.

Under the same conditions, Eq. (19) gives

$$\frac{c_j^{(c)}(t)}{c_0} = 1 - e^{-at}$$

(26)

where

$$a = \frac{N}{t_k} = \frac{v}{(\Delta x)(1 + k)} = \frac{1}{(\Delta t)(1 + k)}$$

(27)

In order to compare this to the results from the Craig model, we consider the output at the finite values $t_k = k \Delta t$, for which

$$\frac{c_j^{(c)}(k)}{c_0} = 1 - e^{-\alpha^2}$$

(28)
Comparing the results for the two kinds of plate models, it is clear that 
\[ e^{-r_k t_k} > 1 - p' \] and therefore \[ e^{-r_k t_k} > (1 - p')k' \]. Consequently \( c_{\text{eff}}(t_k) > c_{\text{eff}}^\text{eq}(t_k) \) for all \( t = t_k \). Thus the Craig effluent is always higher than that from the continuous-flow plate, will reach the initial value faster, and is therefore more efficient. These results are exemplified in Fig. 1, for \( k' = 1 \). Since the argument will extend to any finite number of plates, it is clear that a column composed of a certain number of Craig plates will be more efficient than one composed of an equal number of continuous-flow plates. Thus, when examining experimental data, one must distinguish between descriptions based on Craig plates and continuous-flow plates. In fact, it is better to avoid the term "plate" and speak of Craig segments and continuous-flow segments (these latter might well be called Glueckauf segments). Then no confusion will arise with the experimentally well-defined plate number:

\[
N_{\text{plate}} = \left( \frac{t_k}{\sigma} \right)^2
\]  

(29)

for the effluent peak of any component where \( t_k \) is its retention time (the time of emergence of its center of mass) and \( \sigma \) is its standard deviation (in consistent time units).

The connection between the experimentally determined plate count and the number of plate segments needed to generate exactly this degree of bandspeading has been summarized by Fritz and Scott [21] given earlier as Eqs. (15)

![Fig. 1. Comparison of effluent histories from a single Craig and continuous-flow segment for frontal chromatography (adsorption)](image-url)
and (21). They are repeated here in the present notation for the purposes of comparison:

\[ N_{\text{col}} = N_{\text{plan}} \]  
\[ N_{\text{dis}} = N_{\text{plan}} \left( \frac{k'}{1 + k'} \right) \]  

Thus fewer Craig than Glueckauf segments are needed to generate a certain dispersion; this is consistent with our earlier observation that Craig segments are the more efficient. This also explains the discrepancy described by Glueckauf: when \( k' \approx 1 \), the difference between \( N_{\text{dis}} \) and \( N_{\text{col}} \) is on the order of 100%. It can also be seen from Eq. (31) that when \( k' = 0 \), \( N_{\text{dis}} = 0 \), implying that the Craig model cannot capture the bandspreading of an unretained component. With this exception, however, the Craig model is a useful tool.

Just as the Glueckauf segment can be regarded as a continuous stirred-tank adsorber (CSTA), there is a connection between the Craig segment and a plug flow adsorber (PFA). If we imagine a PFA of length \( \Delta x \) packed with adsorbent into which material is fed from the preceding PFA such that it takes a time \( \Delta t \) to completely fill it, the discretized mass balance is

\[ c(x - \Delta x, t - \Delta t) + \phi(x, t - \Delta t) = c(x, 0) + \phi(x, t) \]  

which is exactly that of the Craig segment.

This also explains the lack of bandspreading in a Craig segment for \( k' = 0 \): the PFA by definition possesses no bandspreading effects in the absence of adsorption. It is only by virtue of finite retention that a series of PFAs, or Craig segments, will generate bandspreading. This is in contrast to the Glueckauf segment wherein bandspreading occurs by mixing over the entire volume of the segment, even in the absence of retention.

3 Results and Discussion

Either plate model described here would seem to be a simple, if approximate, alternative to the detailed rate models. In choosing between them, the fact that the Craig distribution does not predict the dispersion of an unretained solute could argue against it. On the other hand, in the examples given below, this model performs at least as well as the continuous-flow plate model when \( k' \neq 0 \).

One disadvantage of plate models is that they cannot satisfy the Danckwerts boundary conditions [28]. However, it is known that the choice of boundary conditions is only significant when the axial Peclet number is small and the column is relatively short [11]; a combination that occurs infrequently in chromatographic practice. The examples show how the choice of model is largely a matter of convenience.
3.1 Use of Plate Models to Recover Solutions of Rate Models

Rasmussen has derived analytical solutions for detailed rate models of linear chromatography [29, 30]. However, these solutions are complex and involve infinite integrals of oscillatory arguments; simpler approaches that retain sufficient accuracy would be useful in design and scale-up. Here, simulations based on the Craig and continuous-plate models are compared to results from the literature. Theoretical or numerical results were used instead of experimental data in order to assess the difference between the results of the simple and complex models while avoiding the additional scatter that is inherent in experimental data.

Detailed simulations of a complex rate model describing the sorption of a single component on a bidisperse sorbent have been carried out by Haynes and Sharma [8] and Raghavan and Ruthven [31]. Axial dispersion, film mass-transfer, and micro- and macro-pore diffusion are accounted for. A representative result from Raghavan and Ruthven [31] was chosen for comparison to the plate models.

In order to carry out the Craig simulation, the column data (such as dimensions, and values of the various porosities) are used to calculate the volumetric phase ratio from Eq. (3). Since the distribution coefficient $K^*$ is given, the retention factor $k'$ can be calculated ($= \Phi K^*$). The probabilities $p'$ and $q'$ can then be found from Eqs. (10a) and (10b). The chromatographic velocity can be calculated from Eq. (4); this, together with the column length, specifies the column hold-up time. The plate count, $N_{\text{max}}$, can be calculated from Eq. (4). Sometimes data is reported in terms of dimensionless groups other than those used in Eq. (4), but only trivial algebra is needed to calculate the required terms. The number of Craig segments is then calculated from Eq. (31). The (discrete) input pulse width is the final parameter needed. In this case, the effluent history is in dimensionless time units, being scaled to the column hold-up time [31]; then the input pulse width must also be scaled. The concentration is also reported in dimensionless terms, scaled to its input inlet value. With this information, the Craig simulation as expressed by Eq. (14) can be carried out. A FORTRAN program embodying this calculation is given in Appendix II (the parameter values in the program correspond to a later simulation, shown in Fig. 5). The IMSL function for the incomplete beta function is used. This detailed description of how a representative plate simulation was carried out is given only to emphasize the simplicity of the method.

The continuous-flow plate simulation is approached in the same way. The retention time $t_r$ (i.e., the first moment) is calculated from Eq. (1). The input pulse width $t$ (in appropriate units) can be used directly, since time is a continuous variable in this method. The number of continuous-flow segments is calculated from Eq. (30). These parameters are then used in either Eq. (20) or (23).

The results of these simulations were compared to that of Raghavan and Ruthven [31] in Fig. 2; the agreement is excellent.
Fig. 2. Linear elution. Comparison of plate simulations with the numerical results of Raghavan and Rushven [31] for linear elution. The parameter values are: \( \epsilon_i = 0.02, \epsilon_b = 0.32, \epsilon_{lb} = 0.41, K^* = 11.6; \)
\( \text{Pe}_b = \infty, \text{Sh} = 2,000; \delta_{lb} = 3.66 \times 10^{-4}; \text{Pe}_b, \delta_b = 5.06 \times 10^{-3}; N_{\text{plates}} = 200.1 \)

3.1.1 Effect of Sample Volume

Another example of elution chromatography is used to examine the effect of sample volume. Carta [32] used a rate model where pore diffusion was the dominant bandspreading mechanism. His analytical solution for two sample volumes is compared with the results from the plate models in Fig. 3 (a and b). Since a monodisperse pore distribution is assumed, the appropriate retention time equation is not Eq. (1), but the following:

\[
\mu_{L, i} = \frac{L}{u} \left[ \epsilon_i + (1 - \epsilon_i) \epsilon_b + (1 - \epsilon_i)(1 - \epsilon_b)K^*_p \right]
\]

\[
= \frac{L}{u} \left[ \epsilon_i + (1 - \epsilon_i) \left( \epsilon_b + (1 - \epsilon_b)K^*_p \right) \right]
\]

\[
= \frac{L}{v_{\text{in}}} \left[ 1 + \frac{1 - \epsilon_i}{\epsilon_b} K^*_p \right]
\]

(33)

where \( K^*_p = \epsilon_i + (1 - \epsilon_i)K^*_p \) and \( v_{\text{in}} = \frac{u}{\epsilon_b} \).

Carta only reported the lumped value \( K^*_p \) since his system involved a gel, which is unlikely to possess a distinct macroporosity. An analogous form of Eq. (4) is then used to calculate the plate count, with \( \text{Sh} \to \infty \) [11]. The plate simulations can then be carried out as before.
Fig. 3a and b. Linear elution of fractions with large inputs (volume-overloaded elution). Plate simulations are compared to the numerical results of Carta [32]. $c_0 = 0.39; S_b = 89.29; \delta, Pe = 0.231; K^* = 0.66; N_{max} = 152.1$. Feed pulse duration is a 50 s and b 1000 s. Symbols as in Fig. 2.

Again, as can be seen from Fig. 3, the plate models agree well with the more complex rate model. Note that the contribution of the finite widths of the input pulse to the chromatogram (its contribution to the first and second moments is well known, e.g., Sternberg [33]) is automatically accounted for by the solutions used here; no additional correction is needed.
3.1.2 Glucose/Fructose Separation

Since each component can be assigned its own plate number in linear chromatography, plate models can also be used to accurately describe multi-component separations. Fig. 4 shows the comparison of plate simulations with Carta's results on the separation of fructose from glucose [32]. The retention time and plate count were calculated as in Fig. 3. Good agreement is achieved. It may be noted in Fig. 4 that the fructose peak from the rate model [32] does not begin from zero concentration. This is because the rate model was used to model a cyclic separation process; only one cycle was used here in the comparison with the plate models.

3.2 Generalizations of Plate Models

Plate models ensure accurate regeneration of the first and second, but not necessarily of the higher, moments. Skewed peaks (characterized by non-zero third central moments), can be generated from plate models when the plate count is very low ($N_{max} < 20$), but not at the significantly higher plate counts usually found in actual separations. Since skewed peaks emerging from efficient columns tend to indicate nonlinear, rather than linear, chromatography,

![Diagram of Glucose and Fructose Separation](image)

Fig. 4. Multicomponent linear elution. Comparison of plate simulations with the numerical results of Carta [32]. $t_e = 0.39$. For glucose, $S_h = 4.5455; \delta_P = 2.35; K^* = 0.26; N_{max} = 45.5$. For fructose, $S_h = 1.7837; \delta_P = 0.92; K^* = 0.66; N_{max} = 38.2$. Symbols as in Fig. 2
the usefulness of plate models in simulating nonlinear separations is also examined.

3.2.1 Nonlinear Chromatography

The assumption that each component traverses the column independently of the others allowed the effluent history of each component to be calculated separately. Carrying out large-scale separations in the linear mode can be useful in practice when the sorption isotherms stay linear until a relatively high mobile phase concentration, as is frequently the case with sugars. There are, however, some practically important chromatographic modes for which this assumption is no longer valid.

One example is mutual interference caused by high concentrations of the feed components. Here the movement of one component depends on the presence and concentrations of the others, and a common plate count must be used. Such simulations have been widely used by Guiochon and co-workers [e.g., 34, 35] and Snyder and co-workers [e.g. 36, 37]. The usual justification is that the bandspreading suffered by all the feed components is comparable, an assumption which is frequently reasonable for chromatographic separations. In addition, the curvature of the (multicomponent) sorption isotherms also gives rise to bandspreading, since different concentrations will travel with different velocities, and this "thermodynamic contribution to bandspreading" could be a substantial fraction of the total bandspreading. Under these circumstances, plate simulations could still give reasonably accurate results. (The plate models do not have to be extended to account for thermodynamic bandspreading, since it is "built into" the isotherms themselves.)

Another practical instance of interference arises in gradient elution chromatography. Even when the feed components are in the linear regions of their own sorption isotherms, they are influenced by the mobile phase additive (such as salt in ion-exchange chromatography and organic modifier in reversed-phase chromatography) which modulates their retention. Thus the plate count of each feed component varies on moving down the column, since their retention factor varies [38, 39]. It is still possible to approximate the process by a plate simulation, such as the continuous-flow plate model used extensively in this context by Yamamoto et al. [26]. Here the distribution of the mobile phase additive is first solved for (assuming that it is unaffected by the feed components), and this solution is used in the plate simulations of the feed components, where the plate count appropriate to an averaged retention factor is used. In the more complex case where the feed components are also in the nonlinear regions of their own sorption isotherms, the additive will be influenced by the feed, and it would become preferable to simulate the complete rate model. When the modulator is in the nonlinear portion of its own isotherm, peak shapes can be dramatically affected [40]. However, if modulator adsorption is appropriately accounted for, plate simulations can still capture the key features of the chromatogram.
3.2.2 *Non-Equilibrium Phenomena*

Plate models can be generalized to describe specific features. The classical papers by Deuex and Lapidus [23] used a two-dimensional network of plates to describe radial as well as axial dispersion. Returning to the one-space-dimensional description, Villermaux [51] considered a version of the tanks-in-series model in which mass transfer occurs between the mobile and stationary phases (the original form, instantaneous equilibrium is assumed in each tank). The result was

\[
\frac{1}{N_{\text{plate}}} = \frac{1}{N} + \frac{2vL}{k_{\text{eff}}(1 + k')^2} \tag{34}
\]

The plate count from the rate model incorporating axial dispersion and an overall mass transfer coefficient [11] is:

\[
\frac{1}{N_{\text{plate}}} = \frac{2D}{vL} + \frac{2vL}{k_{\text{eff}}(1 + k')^2} \tag{35}
\]

On comparing Eqs. (34) and (35), it can be seen that the mass transfer coefficient \(k_{\text{eff}}\) in the plate model can be directly equated to the overall mass transfer coefficient. This in turn can be set equal to the sum of the individual contributions from film mass transfer, micro- and macro-pore diffusion [8]. The finite nature of the plates must then generate a bandspeading equal only to that produced by axial dispersion in the rate model: \(N = \frac{vL}{2D}\), where \(D\) is the axial dispersion coefficient. This result is to be expected from the rate model, where the mass-transfer and the dispersion contributions to bandspeading are separated. It is an indication of the versatility of plate models that a similar separation is found in Eq. (35).

An additional advantage of plate models is their simplicity in describing the kinetic terms which allow the incorporation of complex equilibrium behavior without resulting in an intractably complex simulation. This has been used to advantage by Wankat [42], who analyzed the interaction of an enzyme with various other components in affinity chromatography. In fact, given that the dominant kinetic contributions in affinity separations is usually slow adsorption-desorption kinetics, it might be appropriate to use an analog of the Villermaux plate model, in which an explicit rate equation for the binding of the substrate is added to the usual mass balance.

Thus, plate models, when used with the appropriate plate height expression, provide a simple and reasonably accurate approach to modeling fixed-bed sorption. Even when a detailed description of the process is required, e.g., in the design of the purification of a high-valued product, such plate simulations could be used as an initial approximation to, and could provide valuable information for, more complex simulations of the coupled PDE's that govern the process.
3.3 Application of Plate Models to Scale-Up

An important advantage of the plate models for linear chromatography is in the relative ease with which they can be applied to scale-up. The rigorous analytical solutions to the complete rate models that have been previously mentioned [29, 30] are complex, and involve infinite integrals with oscillatory arguments. The analytical solutions available for plate models are exact, explicit, and quite simple in form. The use of these solutions scaling separations is outlined next.

The explicit solutions to the Craig model – Eqs. (10) and (11), or (13) and (14) – and the continuous-flow model – Eqs. (19) and (20), or (22) and (23) – can be coupled with the appropriate expression for the plate count, e.g., Eq. (6), to relate the chromatographic effluent histories to the various parameters such as the mass-transfer coefficient and the pore diffusivity that determine band spreading.

The design parameters involved in scale-up are the length and diameter of the column, the particle size (assuming a monodisperse distribution of particles), the volumetric flow rate (or equivalently the mobile phase velocity) and the sample size. The sample composition is usually given. External constraints include the pressure drop and the effluent purity (or, equivalently, the chromatographic resolution). The parameter to be optimized is the throughput or production rate, which are measures of the amounts of acceptably pure material generated per unit time. Mathematically, this can be regarded as a problem in constrained optimization; the explicit dependence in plate solutions of the optimization function on the design parameters should permit rapid numerical solution.

However, in most cases the separation has already been successfully developed at bench-scale. The objective is then to scale the operating parameters such as particle and column size appropriately so as to produce the same separation at preparative-scale. The specification of design parameters on this basis has been studied by several workers [43, 44–46]. The plate models facilitate ready evaluation of such design recommendations.

Figure 5 shows a comparison of large-scale isocratic elution data for the separation of phenylalanine from aspartame taken from Ladisch et al. [47] to results from the Craig model. The various operating parameters, taken from [46], are given in the caption to Fig. 5. The dimensionless parameters representing the contributions of film mass transfer, pore diffusion, etc., are calculated using standard correlations in the literature. The Sherwood number is calculated using the Wilson and Geankoplis correlation [48]. The adsorbate's molecular diffusivity and pore diffusivity are calculated as in Ladisch et al. [47] except that a tortuosity factor of 3 was used. The parameters needed for the Craig simulation were then calculated as described earlier. Thus, a plate calculation involving no fitted parameters is able to achieve reasonable agreement with experiment, as can be seen in Fig. 5. It should be noted that the standard deviation associated with the particle size was 4.9 μm (the particle size itself is 60.3 μm). This size distribution could result in a wider band than would be predicted by the plate model.
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Fig. 5. Scaled-up linear isocratic elution separation of phenylalanine from aspartame; experimental data from Lastoch et al. [47]; Column dimensions: 1.09 x 70 cm; operating temperature: 20°C; flow rate = 2 ml/min; interstitial porosity = 0.36; total porosity = 0.74; feed: 40 ml of 5 mg/ml of both components; particle size = 60.3 µm. Symbols: ○, phenylalanine concentrations from [47]; □, aspartame concentrations from [47]; —— Craig simulation.

4 Conclusions

Plate models are shown to be simple and accurate approximations to detailed rate models in linear chromatography. Regarding a single Craig plate as a PFA explains its lack of bands for an unretained solute, and emphasizes its similarity to a continuous-flow plate (PFA). Both models are shown to be useful in predicting multicomponent separations. Possible application to nonlinear chromatography is discussed. The analytical solutions available for the Craig and continuous-flow plate models are attractive in the scale-up and design of preparative separations.

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5 Appendix I: Solutions to the Craig Model

The basic Craig description (Eq. (8) in the text) is

\[ c(i, j, k) + \phi q(i, j, k) = c(i, j - 1, k - 1) + \phi q(i, j - 1, k - 1) \]  (A1-1)
which can be rewritten for linear chromatography as

$$c(i, j, k) = p_i^{'}c(i, j - 1, k - 1) + q_i^{'}c(i, j, k - 1)$$  (A1-2)

where

$$p_i^{'} = \frac{1}{1 + k_i^{'}}, \quad q_i^{'} = \frac{k_i^{'}}{1 + k_i^{'}}, \quad p_i^{'} + q_i^{'} = 1$$  (A1-3)

This linear partial difference equation can be solved by several methods [15]. Here we use the two-dimensional z-transform [14]. If the z-transform of $c(i, j, k)$ is $U(i, z, w)$, Eq. (A1-2) becomes

$$zw\left[U(i, z, w) - \sum_{j=1}^{\infty} c(i, j, 0)z^{-j} - \sum_{m=1}^{\infty} c(i, 0, k)w^{-m} + c(i, 0, 0)\right]$$

$$= p_i^{'}U(i, z, w) + q_i^{'}z\left[U(i, z, w) - \sum_{m=1}^{\infty} c(i, 0, k)w^{-m}\right]$$  (A1-4)

Letting $c(i, j, k)$ be dimensionless (through division by the input concentration $c_{in}$), the boundary condition for elution chromatography with a finite pulse is

$$c(i, 0, k) = \begin{cases} 1, & 0 \leq k \leq M \\ 0, & k > M \end{cases}$$  (A1-5)

where $M$ represents the (discretized) injection time. The initial condition corresponding to an empty column that agrees with Eq. (A1-5) is

$$c(i, j, 0) = \begin{cases} 1, & j = 0 \\ 0, & j \geq 1 \end{cases}$$  (A1-6)

For frontal chromatography, Eq. (A1-6) remains valid, and the boundary condition is

$$c(i, 0, k) = 1 \quad \text{for all } k \geq 0$$  (A1-7)

Thus, letting $M \to \infty$ in Eq. (A1-5) will give the result for frontal chromatography. Substituting Eqs. (A1-5) and (A1-6) into (A1-4), we have, for elution chromatography,

$$U(i, z, w) = \frac{(zw - q_i^{'}z)}{(zw - q_i^{'}z - p_i^{'})} \sum_{m=0}^{\infty} w^{-m}$$

$$= \frac{1}{1 - \frac{p_i^{'}}{1 - \frac{p_i^{'}}{zw - q_i^{'}}}} \sum_{m=0}^{\infty} w^{-m}$$  (A1-8)

This can be inverted with respect to $z$ to get

$$u(i, j, w) = \frac{p_i^{'}}{w - q_i^{'}} \sum_{m=0}^{\infty} w^{-m}$$  (A1-9)

We note that $m$ is a dummy summation variable, and is analogous to a dummy
integration variable. To invert with respect to \( w \), we rewrite Eq. (A1-9) as
\[
c(i,j,w) = (p_i)^j w^{-j} \left( 1 - \frac{q_i}{w} \right)^{-1} \sum_{m=0}^{-j} w^{-m}
\]
(A1-10)

Inversion can now be carried out to obtain, for \( k - j \geq M \),
\[
c(i,j,k) = (p_i)^j \sum_{m=k-j-M}^{k-j} (-1)^m \binom{-j}{m} (q_i)^m
\]
(A1-11)

where \( \binom{a}{b} \) is the binomial coefficient, given for \( a \geq b \) by \( \binom{a}{b} = \frac{a!}{b!(a-b)!} \).

Using a relation for negative indices in a binomial coefficient [49], there follows
\[
c(i,j,k) = (p_i)^j \sum_{m=k-j-M}^{k-j} \binom{j+m-1}{m} (q_i)^m
\]
(A1-12)

For \( k - j < M \), the solution is
\[
c(i,j,k) = (p_i)^j \sum_{m=0}^{j+m-1} \binom{j+m-1}{m} (q_i)^m
\]
(A1-13)

It can be seen that Eq. (A1-12) represents a finite sum of binomial expressions, as might be expected for a finite pulse input. The corresponding result for frontal chromatography is easily obtained from Eq. (A1-12) by letting \( M \to \infty \):
\[
c_F(i,j,k) = (p_i)^j \sum_{m=0}^{j+m-1} \binom{j+m-1}{m} (q_i)^m
\]
(A1-14)

Eq. (A1-12) and (A1-14) are given in the text as Eq. (10) and (11), where the concentrations have been returned to dimensional form.

6 Appendix II: Computer Program Based on the Craig Model

```plaintext```
implicit real * 8 (a-h, o-z)
real * 8 kprime

data imode = 2/
c
imode = 1 for frontal, = 2 for elution chromatography
data t0, time...in, kprime, plate / 24.2, 202.6, 2.7, 245.0/;
c
0: retention time of an unretained component that fully
c
explores the mobile phase space (i.e., no size exclusion occurs)
c
time...in: the feed volume, in time units
c
kprime: the retention factor of the adsorbate
c
plate: the number of Craig segments (need not be an integer)
```
open (unit = 8, file = 'craig3.mass', status = 'unknown')
delt = d0/plate
p = 1.0d0/(1.0d0 + kprime)
kstart = ifix (plate) + 1
kend = plate + 1250
arg1 = dfloat (plate)
amount = 0.0d0
do 50 k = kstart, kend
time = delt * dfloat (k)
arg2 = dfloat (k) - plate
out1 = dbetai (p, arg1, arg2)
if (mode .eq. 1) amount = amount + out1
if (mode .eq. 2) then
  arg3 = dfloat (k) - time_in - plate
  if (ifix(arg3) .gt. 0) then
    out2 = dbetai (p, arg1, arg3)
  else
    out2 = 0.0d0
  end if
  out1 = out1 - out2
  amount = amount + out1
end if
if ((mode .eq. 1) and. (dabs(out1 - 1.0d0) .gt. 1.0d-6) .and. (out1 .gt. 1.0d-6)) write (6,1000) k, time, out1
if ((mode .eq. 2) and. (out1 .gt. 1.0d-6))
write (6,1000) k, time, out1
n_out = mod (k, 100)
if (n_out .eq. 0) write (8, *) 'k = ', k, ', amount = ', amount
50 continue
stop
1000 format (1x, i5, 2x, g12.5, 3(2x, g20.13))
end
7 References

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