

Linear two-step gradient counter-current chromatography Analysis based on a recursive solution of an equilibrium stage model

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Abstract

The implementation of gradients in continuously operated chromatographic counter-current processes has recently attracted considerable interest as a method to improve the performance of this effective separation method. If liquid mobile phases are applied it is advantageous to set the solvent strength in the desorbent stream higher than that in the feed stream. As a consequence, the components to be separated are more retained in the adsorption zones and more easily eluted in the desorption zones. Due to the additional degrees of freedom the design and the optimization of such a two-step gradient counter-current process is difficult. In this paper a steady state equilibrium stage model is used to simulate the process under linear conditions. A simple solution of the underlying model equations is presented capable to describe efficiently the unit for large stage numbers typically encountered in chromatographic columns. Due to the rapidity of the algorithm developed a broad range of operating conditions can be evaluated systematically for different types of gradients. The impact of (a) the functional dependence of the adsorption equilibrium constants on the solvent composition, (b) the number of equilibrium stages and (c) the specification of purity requirements is illustrated and discussed based on results of parametric calculations. The results achieved emphasize the potential of two-step gradient counter-current chromatography.

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1. Introduction

In the early 1960s the simulated moving bed (SMB) technology was suggested for separations in the petroleum industry [1,2]. In recent years the concept has found several applications in the fine

chemical and pharmaceutical industries where more difficult separations (e.g. enantioseparations) have been performed successfully [3].

To separate mixtures of components which are dissolved in a liquid mobile phase the SMB process is usually implemented using the same solvent to prepare the feed solution and to perform the adsorbent regeneration. Nowadays this so-called isocratic process is well understood and there are reliable design concepts available [4–8]. In analytical chromatography nonisocratic gradient con-

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cepts are known to possess large potential in order to improve separations, mainly to reduce cycle times for discontinuous regimes exploiting repetitive injections [9]. The main idea of applying gradients is to vary the equilibrium distribution functions during the elution process. This can be conveniently done through manipulation of the composition of mixed solvents. The concept of applying gradients in SMB processes has been only recently identified as a powerful method to further improve the separation performance. It was realized that it is in particular attractive to have a solvent in the desorbent stream that is stronger than the solvent containing the feed. Nicoud and co-workers [10,11] suggested applying gradients in SMB processes using a supercritical eluent. In this concept gradients can be implemented by working at different pressure levels. The SMB zone responsible for the desorption of the more retained component operates at the highest mobile phase density, while the zone responsible for adsorption of the less retained component operates at the lowest density level. Due to the fact that the efficient handling of a supercritical eluent at different pressure levels is not a trivial task, the concept has been studied systematically up to now mainly in a laboratory-scale for the separation of model substances [12,13].

Jensen et al. [14] suggested the implementation of a two-step gradient counter-current process using two differently composed liquid mobile phases. Such a concept is easier to implement compared to the application of supercritical eluents. This two-step-gradient process was studied recently in detail theoretically [15] for linear adsorption isotherms exploiting the equilibrium theory. Antos and Seidel-Morgenstern [16,17] presented results of extensive numerical simulations for linear and nonlinear equilibria and a successful experimental test of the two-step gradient principle. Recently, Houwing et al. [18] studied the separation of dilute mixtures of proteins by ion-exchange in simulated moving beds using salt gradients.

In this paper the steady state of a two-step gradient SMB process is studied theoretically based on the well-known analogy to the simpler hypothetical true moving bed (TMB) process. A conventional equilibrium stage model is used to describe the steady state of a TMB unit in which two different solvent composition levels exist. The adsorption isotherms of

the components to be separated are assumed to depend linearly on the solute concentrations. The corresponding Henry constants are considered to be arbitrary nonlinear functions of the local solvent composition.

An essential result of the study is the development of an algorithm that simplifies the calculations for large stage numbers by taking advantage of the structure of the system of model equations. With this rapid algorithm a large set of conditions can be scanned systematically and the influence of all relevant operating parameters on the performance of the process can be evaluated efficiently. Below the model is used to identify suitable operating parameters for different stage numbers, purity requirements and dependencies of the adsorption equilibrium constants on the solvent composition.

2. Principle of a TMB process

The well-known concept of a classical four-zone TMB process is illustrated schematically in Fig. 1 (e.g. [19]). This process is based on the hypothetical assumption that the liquid and solid phases involved are in a real counter-current movement. Thus, the solid phase is also moving continuously. Provided the well-known equivalence relations [4,5] are fulfilled the results of modeling the TMB process closely match the performance of the more complex SMB process which is used in reality. There are two streams entering the TMB unit (Fig. 1): the feed (a mixture of two components A and B) with flow-rate \dot{V}_F and the desorbent or eluent with flow-rate \dot{V}_D . Two streams leave the unit. Under successful conditions one is enriched with the less adsorbable component A (the raffinate stream with flow-rate \dot{V}_R) and one is enriched with the more adsorbable component B (the extract stream with flow-rate \dot{V}_E). The four streams divide the unit into four zones (I, ..., IV). The solid-phase flow-rate of the TMB process, \dot{V}_S , can be simply converted into the corresponding switch time of an equivalent SMB process [4,5]. Each of the four zones has to fulfil distinct tasks. The separation of the two feed components should happen in the two central zones II and III. Here the net flow-rates need to be set in such a way that component A is carried in the direction of the raffinate outlet and component B in the direction of

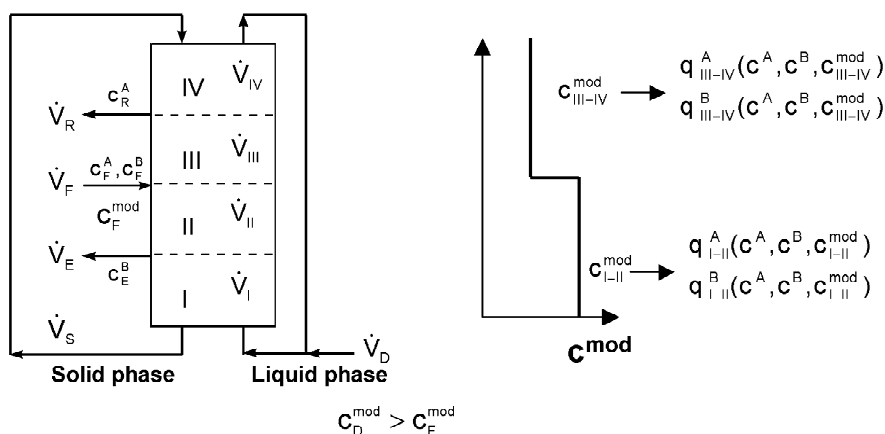


Fig. 1. Principle of the two-step gradient TMB process.

the extract outlet. The desorbent is fed to zone I in order to desorb component B and thus to regenerate the solid phase. Component A is adsorbed on the regenerated solid phase in zone IV in order to regenerate the desorbent.

In the conventional (isocratic) process the solvent strength is identical in the whole unit. The simple idea behind the two-step gradient mode is to set the overall solvent strength in the feed stream lower than that in the desorbent stream. This is realized by using in these two inlet streams different concentrations of a stronger solvent (often called modifier) mixed with a weaker solvent. Thus, the feed is dissolved in a stream with a lower concentration of the modifier compared to the concentration of the modifier in the desorbent stream (i.e. $c_F^{\text{mod}} < c_D^{\text{mod}}$). As the main result, the described functions of both regeneration zones I and IV are fulfilled more efficiently. This allows the reduction of the total solvent amount and leads to less dilution of the products in the raffinate and extract streams. The exploitation of these attractive features is obviously restricted by possible solubility limits.

3. Model of the two-step gradient counter-current process

3.1. Overall mass balances

The essential overall mass balances at the four

characteristic nodes of the TMB unit correlating external and internal flow-rates are (compare Fig. 1):

$$\dot{V}_I = \dot{V}_{IV} + \dot{V}_D \quad (1)$$

$$\dot{V}_{II} = \dot{V}_I - \dot{V}_E \quad (2)$$

$$\dot{V}_{III} = \dot{V}_{II} + \dot{V}_F \quad (3)$$

$$\dot{V}_{IV} = \dot{V}_{III} - \dot{V}_R \quad (4)$$

In the above, \dot{V}_i represents the internal volumetric liquid phase flow-rate in zone *i*. \dot{V}_F , \dot{V}_D , \dot{V}_R , and \dot{V}_E are the external volumetric flow-rates for dosing feed or desorbent and for withdrawing raffinate or extract.

If gradients are applied one can specify as additional free parameters the two different modifier concentrations in the feed, c_F^{mod} , and in the desorbent, c_D^{mod} (with $c_F^{\text{mod}} < c_D^{\text{mod}}$). If the modifier does not interact with the solid phase (i.e. if it is not adsorbable), two distinct and constant modifier concentration levels will establish in the unit. In Zones I and II a “strong” solvent with the modifier concentration c_{I-II}^{mod} will be present, and in zones III and IV a “weak” solvent with the modifier concentration c_{III-IV}^{mod} will be present. The equations required to calculate these concentrations follow directly from the modifier mass balances at the two stages where this component is introduced:

$$c_{I-II}^{\text{mod}} = \frac{\dot{V}_F \dot{V}_{IV} c_F^{\text{mod}} + \dot{V}_D \dot{V}_{III} c_D^{\text{mod}}}{\dot{V}_I \dot{V}_{III} - \dot{V}_{II} \dot{V}_{IV}} \quad (5)$$

$$c_{\text{III-IV}}^{\text{mod}} = \frac{\dot{V}_F \dot{V}_I c_F^{\text{mod}} + \dot{V}_D \dot{V}_{\text{II}} c_D^{\text{mod}}}{\dot{V}_I \dot{V}_{\text{III}} - \dot{V}_{\text{II}} \dot{V}_{\text{IV}}} \quad (6)$$

3.2. Equilibrium stage model

To describe the migration of dissolved components within chromatographic columns it can be usually assumed that there are isothermal conditions. To perform difficult separations such columns are well packed with small particles of the stationary phase. Thus, the corresponding equilibrium stage numbers are relatively high (typically several thousands [20]). A convenient and useful way to simulate such separation processes is to assume permanently established local equilibria between the two phases. Based on this assumption a simple equilibrium stage model is proposed below in order to describe TMB processes under gradient conditions. One equilibrium stage j is illustrated in Fig. 2. Under steady state conditions for this stage located in zone i the following mass balance equation holds for a component k :

$$\dot{V}_S q_{i,j+1}^k (\bar{c}_{i,j+1}) + \dot{V}_i c_{i,j-1}^k - \dot{V}_i c_{i,j}^k - \dot{V}_S q_{i,j}^k (\bar{c}_{i,j}) = \dot{V}_{\text{ext}} c_{\text{ext}}$$

$$\text{with } \dot{V}_{\text{ext}} c_{\text{ext}} = \begin{cases} -\dot{V}_F c_F^k & \text{for } j = \text{F} \\ -\dot{V}_D c_D^k & \text{for } j = \text{D} \\ \dot{V}_R c_R^k & \text{for } j = \text{R} \\ \dot{V}_E c_E^k & \text{for } j = \text{E} \\ 0 & \text{for all other } j \end{cases}$$

$$i = \text{I, II, III, IV} \quad j = 1, N_{\text{total}} \quad k = \text{A, B} \quad (7)$$

In the above $c_{i,j}^k$ is the liquid-phase concentration of component k in stage j and zone i , $q_{i,j}^k$ is the corresponding solid-phase concentration in equilib-

rium with the liquid phase and the c_F^k , c_D^k , c_R^k and c_E^k are the solute concentrations in the corresponding external streams.

Fig. 3 shows the series connection of all stages forming the TMB unit arranged as a ring. The four zones of the TMB are assumed to possess N_I , N_{II} , N_{III} and N_{IV} equilibrium stages. By choosing different N_i values zones of different length can be simulated. The zones are connected through the raffinate (R), feed (F), extract (E) and desorbent (D) stages. Thus, the total number of equilibrium stages is:

$$N_{\text{total}} = 4 + N_I + N_{\text{II}} + N_{\text{III}} + N_{\text{IV}} \quad (8)$$

For nonlinear and coupled adsorption isotherms, $q^A(c^A, c^B)$ and $q^B(c^A, c^B)$, the system of algebraic Eqs. (7) can be solved only numerically.

In order to study essential features of the two-step gradient TMB process in a simple manner, it is expedient to analyze the special case of linear adsorption isotherms that are specific for each component and do not depend on the concentrations of other components:

$$q^k = K^k c^k \quad \text{with } K^A < K^B \quad k = \text{A, B} \quad (9)$$

Thus, in the gradient process there are for each component A and B two internal Henry constants which are related to the two local modifier concentration levels in zones I–II and zones III–IV:

$$K_{\text{I-II}}^k = K_{\text{I-II}}^k (c_{\text{I-II}}^{\text{mod}}) \quad \text{and} \\ K_{\text{III-IV}}^k = K_{\text{III-IV}}^k (c_{\text{III-IV}}^{\text{mod}}) \quad k = \text{A, B} \quad (10)$$

To further simplify the discussion it is useful to introduce for each zone i a dimensionless factor χ_i

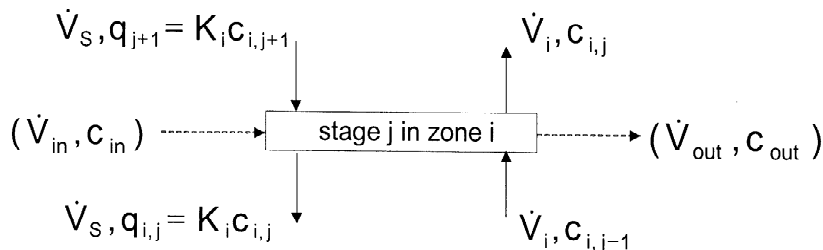


Fig. 2. Mass balance for a single stage (incoming and outgoing streams have to be considered only for the four distinct stages F, R, D and E).

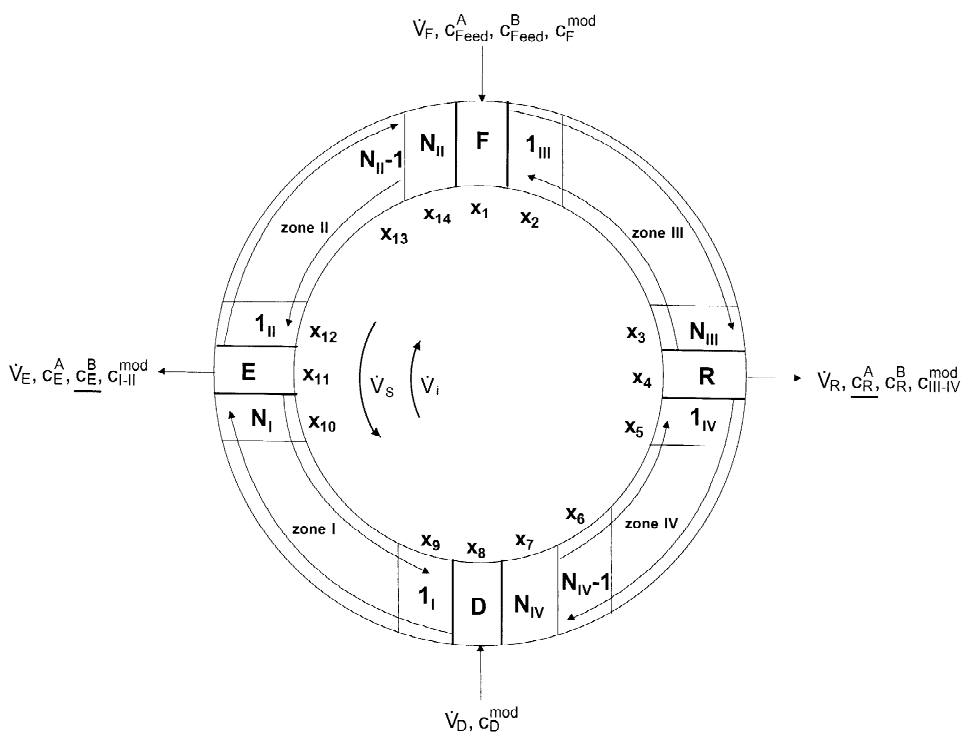


Fig. 3. Discretisation of the TMB unit and definition of 14 characteristic stages.

expressing the ratio of the flow-rates in the two phases:

$$\chi_i^k = \frac{\dot{V}_i}{\dot{V}_S K_{ii}^k} \quad i, ii = \begin{cases} \text{I, I-II} \\ \text{II, I-II} \\ \text{III, III-IV} \\ \text{IV, III-IV} \end{cases} \quad k = \text{A, B} \quad (11)$$

For linear uncoupled adsorption isotherms the calculations presented below can be performed independently for the two components A and B. Thus, below the index k will be omitted.

With Eqs. (9) and (11) the balance Eq. (7) can be expressed as:

$$c_{i,j+1} + \chi_i c_{i,j-1} - \chi_i c_{i,j} - c_{i,j} = \frac{\dot{V}_{\text{ext}} c_{\text{ext}}}{\dot{V}_S K_{ii}}$$

$$i, ii = \begin{cases} \text{I, I-II} \\ \text{II, I-II} \\ \text{III, III-IV} \\ \text{IV, III-IV} \end{cases} \quad j = 1, N_{\text{total}} \quad (12)$$

The system of Eqs. (12) can be solved with the conventional standard methods of linear algebra in order to determine for given operating parameters the concentrations of components A and B in the outlet streams and the whole internal concentration profiles. However, for large stage numbers N_{total} it is advantageous to simplify the calculation by exploiting the specific structure of Eq. (12).

3.3. Simplified solution according to Kremser

Below an efficient algorithm is presented capable of solving Eq. (12). It is based on an adaptation of the recursion technique suggested by Kremser [21] to analyze multistage counter-current absorption processes. To derive the essential equations Fig. 4 presents a part of one TMB zone i which might consist of a relative large number of stages M_i . It will be shown below that instead of performing a time consuming stage by stage calculation it is possible to “jump” over all these M_i stages. This

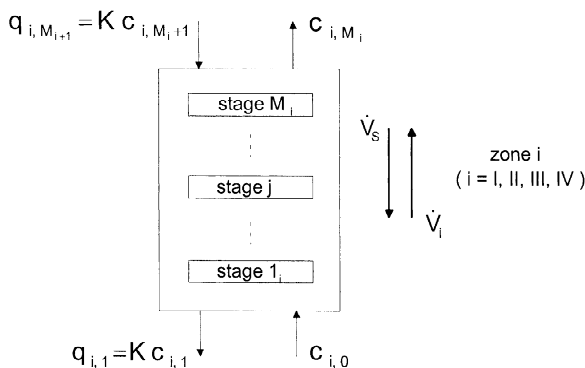


Fig. 4. Illustration of M_i stages in zone i in order to derive Eqs. (21) and (22).

becomes obvious if the following balance equations are considered.

For the first stage ($j = 1$) it holds:

$$c_{i,2} + \chi_i c_{i,0} - \chi_i c_{i,1} - c_{i,1} = 0 \quad (13)$$

This equation can be rearranged in order to determine $c_{i,2}$

$$\begin{aligned} c_{i,2} &= \chi_i c_{i,1} + c_{i,1} - \chi_i c_{i,0} \\ &= (\chi_i + 1) c_{i,1} - \chi_i c_{i,0} \end{aligned} \quad (14)$$

Analogously, the overall balance equation for the first two stages ($j = 1$ and 2) is:

$$c_{i,3} + \chi_i c_{i,0} - \chi_i c_{i,2} - c_{i,1} = 0 \quad (15)$$

Rearrangement and insertion of Eq. (14) leads to the following expression for $c_{i,3}$:

$$\begin{aligned} c_{i,3} &= \chi_i c_{i,2} + c_{i,1} - \chi_i c_{i,0} \\ &= (\chi_i^2 + \chi_i + 1) c_{i,1} - (\chi_i^2 + \chi_i) c_{i,0} \end{aligned} \quad (16)$$

Balancing over the first three stages ($j = 1, 2$ and 3) obviously gives:

$$c_{i,4} + \chi_i c_{i,0} - \chi_i c_{i,3} - c_{i,1} = 0 \quad (17)$$

$$\begin{aligned} c_{i,4} &= \chi_i c_{i,3} + c_{i,1} - \chi_i c_{i,0} \\ &= (\chi_i^3 + \chi_i^2 + \chi_i + 1) c_{i,1} - (\chi_i^3 + \chi_i^2 + \chi_i) c_{i,0} \end{aligned} \quad (18)$$

Generalizing the above leads for M_i stages to the following overall balance:

$$c_{i, M_i+1} + \chi_i c_{i,0} - \chi_i c_{i, M_i} - c_{i,1} = 0 \quad (19)$$

$$\begin{aligned} c_{i, M_i+1} &= (\chi_i^{M_i} + \chi_i^{M_i-1} + \dots + \chi_i + 1) c_{i,1} \\ &\quad - (\chi_i^{M_i} + \chi_i^{M_i-1} + \dots + \chi_i^2 + \chi_i) c_{i,0} \end{aligned} \quad (20)$$

The summations of the terms with χ_i can be simplified significantly leading to:

$$\begin{aligned} c_{i, M_i+1} &= \gamma_i c_{i,1} - (\gamma_i - 1) c_{i,0} \quad \text{with} \\ \gamma_i &= \frac{\chi_i^{M_i+1} - 1}{\chi_i - 1} \quad i = \text{I, II, III, IV} \end{aligned} \quad (21)$$

In an analogous manner a similar expression can be derived if the recursive analysis is started at stage M_i and oriented in the opposite direction towards stage 1:

$$\begin{aligned} c_{i,0} &= \eta_i c_{i, M_i} - (\eta_i - 1) c_{i, M_i+1} \quad \text{with} \\ \eta_i &= \frac{\chi_i^{-M_i+1} - 1}{\chi_i^{-1} - 1} \quad i = \text{I, II, III, IV} \end{aligned} \quad (22)$$

Eqs. (21) and (22) provide two balance equations allowing to analyze efficiently all four TMB zones. In these two equations the border stages 1 and M_i are only connected with the two external stages 0 and $M_i + 1$. Thus, in order to calculate the concentrations $c_{i,1}$ and c_{i, M_i} one does not necessarily need to determine the concentrations at all internal stages 2 to $M_i - 1$. To take maximum advantage of this possible lumping it is expedient to set for all four zones the M_i according to the zone stage numbers N_i . This is unrestrictedly feasible for the description of an isocratic TMB process where K_{ii} is identical for all zones. In case of the two-step gradient process K_{ii} changes its value at the stages F and D. Thus, Eqs. (21) and (22) could be exploited in zones II and IV only up to $M_{II} = N_{II} - 1$ and $M_{IV} = N_{IV} - 1$ (Fig. 3). For stage N_{II} in zone II and stage N_{IV} in zone IV the following additional balance equations hold:

$$\begin{aligned} \text{stage } N_{II}: \\ c_F + \frac{\dot{V}_{II}}{\dot{V}_S K_{III-IV}} \cdot c_{II, N_{II}-1} - \left(\frac{K_{I-II}}{K_{III-IV}} + \frac{\dot{V}_{II}}{\dot{V}_S K_{III-IV}} \right) \\ \cdot c_{II, N_{II}} = 0 \end{aligned} \quad (23)$$

stage N_{IV} :

$$c_D + \frac{\dot{V}_{IV}}{V_S K_{I-II}} \cdot c_{IV,N_{IV-1}} - \left(\frac{K_{III-IV}}{K_{I-II}} + \frac{\dot{V}_{IV}}{V_S K_{I-II}} \right) \cdot c_{IV,N_{IV}} = 0 \quad (24)$$

For the complete mathematical description of all stages of the TMB unit it remains to specify the four balance equations valid for the feed, raffinate, desorbent and extract stages. These equations are:

stage F:

$$c_{III,1_{III}} + \frac{\dot{V}_{II}}{\dot{V}_S K_{III-IV}} \cdot c_{II,N_{II}} - (1 + \chi_{III}) c_F = - \frac{\dot{V}_F}{\dot{V}_S K_{III-IV}} \cdot c_{Feed} \quad (25)$$

stage R:

$$c_{IV,1_{IV}} + \chi_{III} c_{III,N_{III}} - \left(1 + \chi_{IV} + \frac{\dot{V}_R}{\dot{V}_S K_{III-IV}} \right) \cdot c_R = 0 \quad (26)$$

stage D:

$$c_{I,1_I} + \frac{\dot{V}_{IV}}{\dot{V}_S K_{I-II}} \cdot c_{IV,N_{IV}} - (1 + \chi_I) c_D = 0 \quad (27)$$

stage E:

$$c_{II,1_{II}} + \chi_I c_{I,N_I} - \left(1 + \chi_{II} + \frac{\dot{V}_E}{\dot{V}_S K_{I-II}} \right) \cdot c_E = 0 \quad (28)$$

Eqs. (21)–(28) form a system of 14 linear equations for 14 distinct concentrations in the TMB unit. If these unknown concentrations are numbered x_1, x_2, \dots, x_{14} according to their consecutive arrangement starting with c_F (see Fig. 3 and Table 1) the following system of 14 linear equations results:

stage F [Eq. (25)]:

$$-(1 + \chi_{III}) x_1 + x_2 + \beta \chi_{II} x_{14} = -\chi_F c_{Feed} \quad (29)$$

stage 1_{III} [Eq. (21)]:

$$(\gamma_{III} - 1)x_1 - \gamma_{III}x_2 + x_4 = 0 \quad (30)$$

stage N_{III} [Eq. (22)]:

$$x_1 - \eta_{III}x_3 + (\eta_{III} - 1)x_4 = 0 \quad (31)$$

stage R [Eq. (26)]:

$$\chi_{III}x_3 - (1 + \chi_{IV} + \chi_R)x_4 + x_5 = 0 \quad (32)$$

stage 1_{IV} [Eq. (21)]:

$$(\gamma_{IV} - 1)x_4 - \gamma_{IV}x_5 + x_7 = 0 \quad (33)$$

stage N_{IV-1} [Eq. (22)]:

$$x_4 - \eta_{IV}x_6 + (\eta_{IV} - 1)x_7 = 0 \quad (34)$$

stage N_{IV} [Eq. (24)]:

$$\alpha \chi_{IV}x_6 - \alpha(1 + \chi_{IV})x_7 + x_8 = 0 \quad (35)$$

stage D [Eq. (27)]:

$$\alpha \chi_{IV}x_7 - (1 + \chi_I)x_8 + x_9 = 0 \quad (36)$$

stage 1_I [Eq. (21)]:

$$(\gamma_I - 1)x_8 - \gamma_Ix_9 + x_{11} = 0 \quad (37)$$

stage N_I [Eq. (22)]:

$$x_8 - \eta_Ix_{10} + (\eta_I - 1)x_{11} = 0 \quad (38)$$

stage E [Eq. (28)]:

$$\chi_Ix_{10} - (1 + \chi_{II} + \chi_E)x_{11} + x_{12} = 0 \quad (39)$$

stage 1_{II} [Eq. (21)]:

$$(\gamma_{II} - 1)x_{11} - \gamma_{II}x_{12} + x_{14} = 0 \quad (40)$$

stage N_{II-1} [Eq. (22)]:

$$x_{11} - \eta_{II}x_{13} + (\eta_{II} - 1)x_{14} = 0 \quad (41)$$

Table 1

Notation for the 14 unknown concentrations used in Eqs. (29)–(42) (compare Fig. 3)

x_1	x_2	x_3	x_4	x_5	x_6	x_7	x_8	x_9	x_{10}	x_{11}	x_{12}	x_{13}	x_{14}
c_F	$c_{III,1_{III}}$	$c_{III,N_{III}}$	c_R	$c_{IV,1_{IV}}$	$c_{VI,N_{IV-1}}$	$c_{IV,N_{IV}}$	c_D	$c_{I,1_I}$	c_{I,N_I}	c_E	$c_{II,1_{II}}$	$c_{II,N_{II-1}}$	$c_{II,N_{II}}$

fully applied to correlate retention parameters in various chromatographic systems [25]. The parameters of Eq. (44) must be determined for a concrete system based on experimental investigations.

4. Flow-rate ratios and separation regions according to equilibrium theory

Up to now the prediction of the two outlet concentrations c_E and c_R and the calculation of the corresponding concentration profiles within the TMB was considered for given operating parameters was considered. The more challenging task in the stage of designing such counter-current processes is of course to find suitable operating parameters allowing to achieve certain goals. This problem will not be discussed in depth here. An excellent analysis of this issue was recently published by Abel et al. [15]. The approach is based on identifying parameter regions where a complete separation can be achieved. Such regions can be conveniently expressed in terms of dimensionless flow-rate ratios, m_i , defined by Mazzotti et al. [6] and Abel et al. [15] as follows:

$$m_i = \frac{\dot{V}_i}{\dot{V}_S} \quad i = \text{I, II, III, IV} \quad (45)$$

Assuming an infinite number of stages the equilibrium theory allows to derive explicit boundaries for the four flow-rate ratios that need to be fulfilled in order to guarantee the functioning of all zones and thus, allowing for complete separation. For linear isotherms and isocratic conditions the flow-rate ratios must fulfil the following inequalities:

$$\begin{aligned} m_{\text{IV}} &< K^{\text{A}} \\ K^{\text{A}} &< m_{\text{II}} < m_{\text{III}} < K^{\text{B}} \\ K^{\text{B}} &< m_{\text{I}} \end{aligned} \quad (46)$$

For the two-step gradient process considered here one has to take into account the two levels for the Henry constants and it holds:

$$\begin{aligned} m_{\text{IV}} &< K_{\text{III-IV}}^{\text{A}}(c_{\text{III-IV}}^{\text{mod}}) \\ K_{\text{III-IV}}^{\text{A}}(c_{\text{III-IV}}^{\text{mod}}) &< m_{\text{III}} < K_{\text{III-IV}}^{\text{B}}(c_{\text{III-IV}}^{\text{mod}}) \\ K_{\text{I-II}}^{\text{A}}(c_{\text{I-II}}^{\text{mod}}) &< m_{\text{II}} < K_{\text{I-II}}^{\text{B}}(c_{\text{I-II}}^{\text{mod}}) \\ K_{\text{I-II}}^{\text{B}}(c_{\text{I-II}}^{\text{mod}}) &< m_{\text{I}} \end{aligned} \quad (47)$$

It is instructive to draw the regions where complete separation is possible in a $m_{\text{II}}-m_{\text{III}}$ plane. For isocratic conditions these regions are triangular and fixed by the two Henry constants [6]. For the two-step gradient situation the determination of these regions is more complex since Eq. (47) has to be fulfilled together with all mass balance Eqs. (1)–(6). Abel et al. [15] gave the theoretical framework to calculate analytically for $N \rightarrow \infty$ regions guaranteeing 100% purity. The results presented by Abel et al. [15] were used in this work to check the accuracy of the equilibrium stage model and the solution algorithm presented above. For this the following similarity between the m_i (Eq. (45)) and the χ_i introduced above [Eq. (11)] had to be respected:

$$m_i = \frac{\chi_i}{K_{ii}} \quad i, ii = \begin{cases} \text{I, I-II} \\ \text{II, I-II} \\ \text{III, III-IV} \\ \text{IV, III-IV} \end{cases} \quad (48)$$

In contrast to the analytical solutions valid for the case of infinite efficiency and complete separation derived by Abel et al. [15] the model studied in our work is also capable of analysing the process for lower stage numbers and reduced purity requirements. Thus, the impact of these two parameters can be investigated.

5. Calculations performed and results

The first goal of the calculations performed was to compare the results for high efficiencies and high purity with the available analytical solutions for $N \rightarrow \infty$ and $\text{Pur}=1$. This comparison could be conveniently done by comparing the separation regions in the $m_{\text{II}}-m_{\text{III}}$ plane as a function of the two new free parameters of the gradient process $c_{\text{F}}^{\text{mod}}$ and $c_{\text{D}}^{\text{mod}}$. Due to the rapidity of the algorithm it can be used to scan in a short time over the four remaining operating parameters. Instead of using directly the four flow-rate ratios m_i , the following explicit strategy was applied. In the two outer calculation loops the two internal modifier concentration levels were scanned. For these just the following simple constraints need to be respected: $c_{\text{F}}^{\text{mod}} < c_{\text{III-IV}}^{\text{mod}} < c_{\text{I-II}}^{\text{mod}} < c_{\text{D}}^{\text{mod}}$. In the two inner calculation loops m_{II} and m_{IV} were varied

within reasonable regions that could be easily estimated from the Henry constants corresponding to the two inlet modifier concentrations. The remaining two flow-rate ratios could be finally specified from the modifier balance Eqs. (5) and (6). For each operating point the purity of the two outlets was calculated from the corresponding extract and raffinate concentrations according to:

$$\text{Pur}_{\text{Port}}^k = \frac{c_{\text{Port}}^k}{c_{\text{Port}}^A + c_{\text{Port}}^B} \quad \text{with } k = A, B, \quad (49)$$

Port = E, R

In this way all acceptable points could be plotted in the $m_{\text{II}} - m_{\text{III}}$ plane. For the regions identified there are no constraints concerning the other two flow-rate ratios.

The results of studying the two-step gradient TMB process with the equilibrium stage model will be presented below for four different sets of parameters in the adsorption isotherm model given with Eq. (44). The applied parameters are summarized in Table 3.

5.1. Set 1 (isocratic case)

The parameters of set 1 correspond to a simple

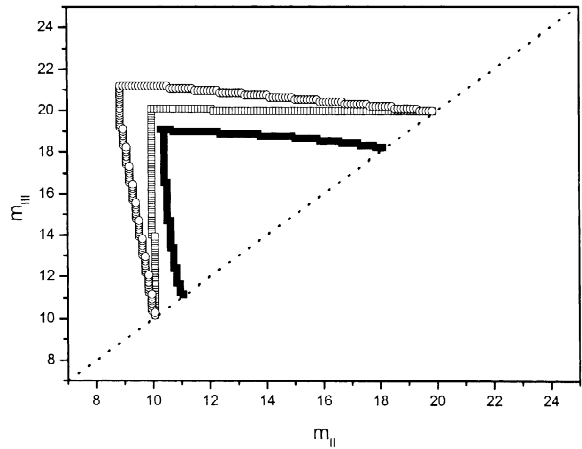


Fig. 5. Influence of the total stage numbers N_{total} and of the specified purity requirements Pur on the size of the separation region in the $m_{\text{II}} - m_{\text{III}}$ plane for parameters set 1 (isocratic conditions). (a) $N_{\text{total}} = 4004$, $\text{Pur}_{\text{Raff}}^A$ and $\text{Pur}_{\text{Ext}}^B > 0.99$ (region in middle); (b) $N_{\text{total}} = 204$, $\text{Pur}_{\text{Raff}}^A$ and $\text{Pur}_{\text{Ext}}^B > 0.99$ (smallest region); (c) $N_{\text{total}} = 4004$; $\text{Pur}_{\text{Raff}}^A$ and $\text{Pur}_{\text{Ext}}^B > 0.9$ (largest region).

isocratic situation and served as a first test of the algorithm. The analytical solution is a triangle in the $m_{\text{II}} - m_{\text{III}}$ plane fixed at the two Henry constants which are 10 and 20 for the case studied. Fig. 5 shows that this result is achieved after the scanning

Table 3
Four sets of adsorption isotherm parameters according to Eq. (44)

Set	Component k	K_0^k	a^k	b^k	Results in Figs.
1	A	10	1	0	5
	B	20	1	0	
2 ^a	A	28.2 [1.41] ^a	1	19 [0.95] ^a	6 and 7
	B	42.4 [2.12] ^a	1	19 [0.95] ^a	
3 ^a	A	14.1 [1.41] ^a	1	9 [0.9] ^a	8 and 9
	B	7.067 [2.12] ^a	1	2.333 [0.7] ^a	
4	A	0.5	0	1	10 and 11
	B	1	0	1	

^a Equation used in a different form by Abel et al. [15]:

$$K_{\text{Ab}}^k = \frac{K_{0,\text{Ab}}^k}{[1 - b_{\text{Ab}}^k(1 - c^{\text{mod}})]}, c^{\text{mod}} \leq 1.$$

Correlation between parameters in Eq. (44) and parameters defined above (given in brackets):

$$K_{0,\text{Ab}}^k = \frac{K_0^k}{1 + b^k}, b_{\text{Ab}}^k = \frac{b^k}{1 + b^k}.$$

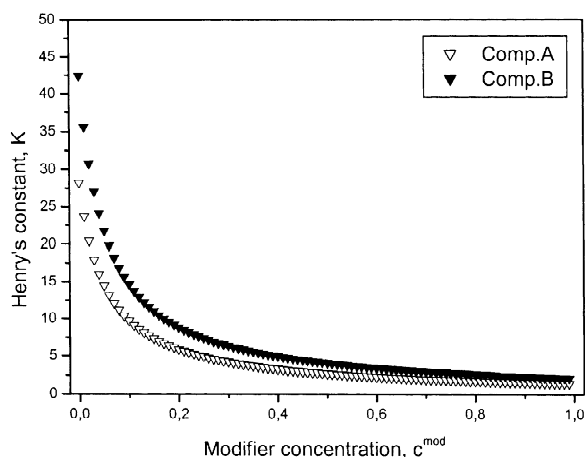


Fig. 6. Dependence of the Henry constants for components A and B as a function of the modifier concentration according to Eq. (44) (parameter set 2, Table 3).

process for $N = 1000$ (for each zone) selecting all points for which the purity of both outlets is above 0.99. The results indicate the correctness of the developed algorithm. Reducing the number of stages leads to a shrinking of the region. Since the more

efficient points are more remote of the diagonal the process productivity is reduced. Reducing on the other hand the requirements on product purity favorably increases the size of the separation region.

5.2. Sets 2 and 3

The parameters of sets 2 and 3 correspond to values used in the work of Abel et al. [15]. The strong influence of the modifier concentration on the Henry constants of the two components is illustrated in Fig. 6. Fig. 7 presents the results of the scanning process for these isotherms. The analytical solution given by Abel et al. [15] for $N \rightarrow \infty$ and $\text{Pur} = 1$ is also presented as a solid line. Again a good agreement was found, as exemplified in Fig. 7a. The transformation of the shape of the separation region due to the gradient compared to the isocratic situation (Fig. 5) is obvious. The effects of reducing the stage number and reducing the purity requirements shown in Fig. 7b also correspond to the isocratic case. In Fig. 7a also the effect of decreasing the modifier content in the desorbent (from 1 to 0.25) is illustrated. As a consequence of the resulting higher adsorbability the separation region is shifted towards

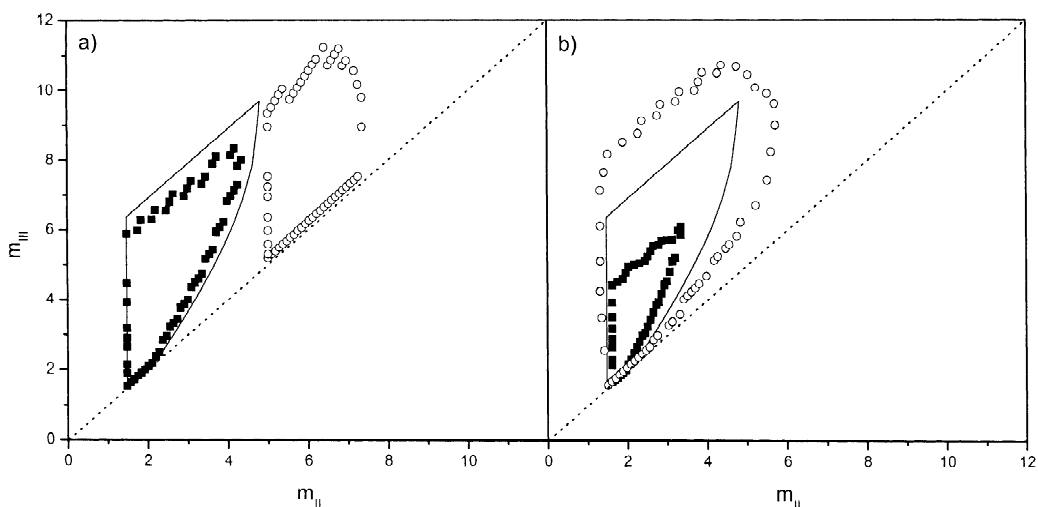


Fig. 7. Separation regions for parameter set 2 (Table 3) and $c_F^{\text{mod}} = 0.1$, $c_D^{\text{mod}} = 1.0$. Solid lines: Analytical solution of Abel et al. [15] for $\text{Pur}_{\text{Raff}}^{\text{A}} = \text{Pur}_{\text{Extr}}^{\text{B}} = 1$ and $N_{\text{total}} \rightarrow \infty$. Points: Results for stage model for (a) $\text{Pur}_{\text{Raff}}^{\text{A}}$ and $\text{Pur}_{\text{Extr}}^{\text{B}} > 0.9999$ and $N_{\text{total}} = 4004$ (closed symbols). The open symbols in (a) correspond to $c_D^{\text{mod}} = 0.25$. Results for (b): $\text{Pur}_{\text{Raff}}^{\text{A}}$ and $\text{Pur}_{\text{Extr}}^{\text{B}} > 0.9999$ and $N_{\text{total}} = 404$ (closed symbols), $\text{Pur}_{\text{Raff}}^{\text{A}}$ and $\text{Pur}_{\text{Extr}}^{\text{B}} > 0.85$ and $N_{\text{total}} = 4004$ (open symbols).

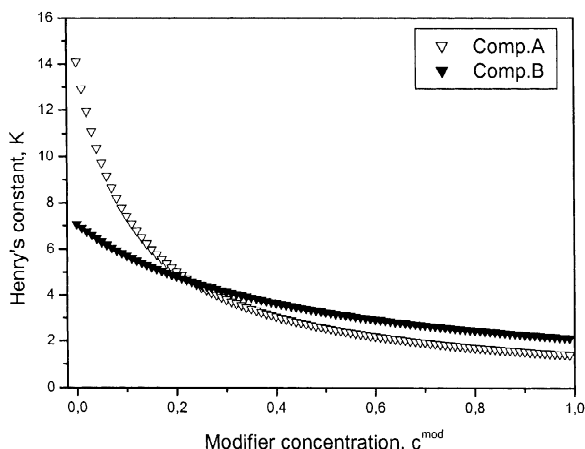


Fig. 8. Dependence of the Henry constants for components A and B as a function of the modifier concentration according to Eq. (44) (parameter set 3, Table 3).

larger $m_{\text{II}} - m_{\text{III}}$ values. Similar results were achieved for parameter set 3. For this set the isotherms intersect each other as shown in Fig. 8. This leads to completely other shapes of the separation regions. Again the agreement with the analytical solutions is satisfactorily for a high stage number and high purity (Fig. 9a and b).

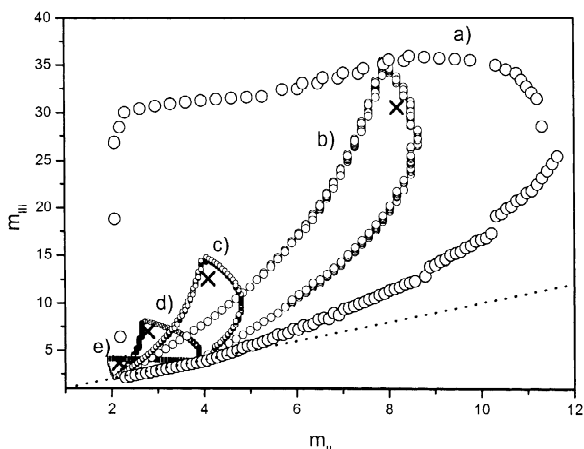


Fig. 10. Separation regions for parameter set 4 (Table 3). $\text{Pur}_{\text{Raff}}^{\text{A}} = \text{Pur}_{\text{Extr}}^{\text{B}} > 0.95$, $N_{\text{total}} = 404$. (a) $c_{\text{F}}^{\text{mod}} = 0.02$, $c_{\text{D}}^{\text{mod}} = 0.25$; (b) $c_{\text{F}}^{\text{mod}} = 0.02$, $c_{\text{D}}^{\text{mod}} = 0.25$; (c) $c_{\text{F}}^{\text{mod}} = 0.05$, $c_{\text{D}}^{\text{mod}} = 0.25$; (d) $c_{\text{F}}^{\text{mod}} = 0.1$, $c_{\text{D}}^{\text{mod}} = 0.25$; (e) $c_{\text{F}}^{\text{mod}} = c_{\text{D}}^{\text{mod}} = 0.25$ (isocratic case). For cases (b)–(e) the following constraints were used: $\varphi_1 = \varphi_{\text{IV}} = 1.1$ [Eqs. (50) and (51)]. Crosses mark operating points used for generating Fig. 11.

5.3. Set 4

Fig. 10 shows the separation regions corresponding to parameter set 4. The systematic scanning

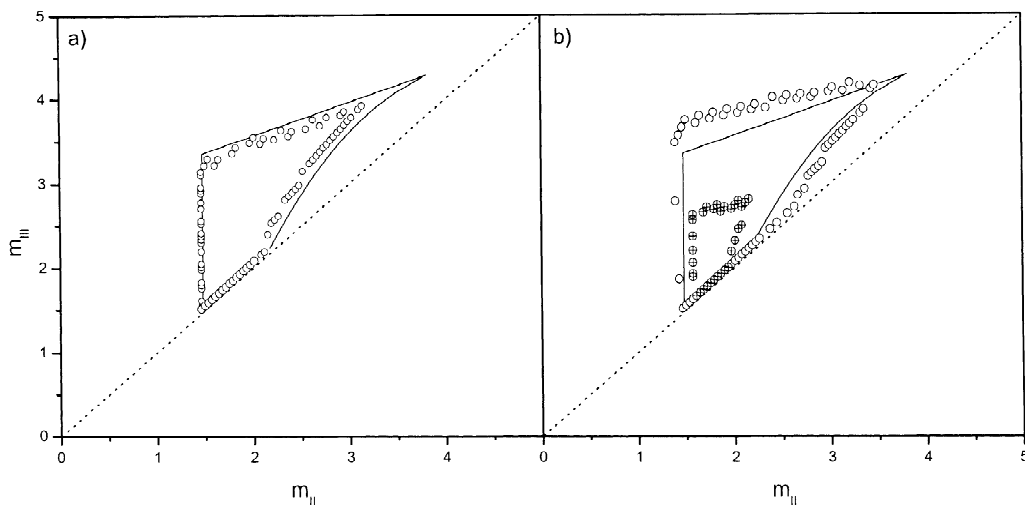


Fig. 9. Separation regions for parameter set 3 (Table 3) and $c_{\text{F}}^{\text{mod}} = 0.1$, $c_{\text{D}}^{\text{mod}} = 1.0$. Solid lines: Analytical solution of Abel et al. [15] for $\text{Pur}_{\text{Raff}}^{\text{A}} = \text{Pur}_{\text{Extr}}^{\text{B}} = 1$ and $N_{\text{total}} \rightarrow \infty$. Points: Results for stage model for (a) $\text{Pur}_{\text{Raff}}^{\text{A}}$ and $\text{Pur}_{\text{Extr}}^{\text{B}} > 0.9999$ and $N_{\text{total}} = 4004$; (b) $\text{Pur}_{\text{Raff}}^{\text{A}}$ and $\text{Pur}_{\text{Extr}}^{\text{B}} > 0.9999$ and $N_{\text{total}} = 404$ (filled symbols) and $\text{Pur}_{\text{Raff}}^{\text{A}}$ and $\text{Pur}_{\text{Extr}}^{\text{B}} > 0.85$ and $N_{\text{total}} = 4004$ (open symbols).

over four free parameters [region (a)] is no problem with the efficient algorithm developed. Unfortunately this tool is available only for linear systems. Non-linear systems have to be analysed numerically as presented e.g. by Antos and Seidel-Morgenstern [17]. In general to avoid time consuming calculations it is possible to reduce the parameter space by fixing two parameters e.g. m_I and m_{IV} and scanning only over the remaining two (m_{II} and m_{III}). In this way of course not the complete separation region can be found. An example for this approach is to specify two safety factors φ_I and φ_{IV} (both >1) and to calculate m_I and m_{IV} according to:

$$m_I = \varphi_I K_{I-II}^B \tag{50}$$

$$m_{IV} = \frac{K_{III-IV}^A}{\varphi_{IV}} \tag{51}$$

Now for each pair of m_{II} and m_{III} all remaining operating parameters can be calculated iteratively as discussed by Antos and Seidel-Morgenstern [16]. Subsequently the purity of the two outlets can be determined with the algorithm described above. In Fig. 10 is shown the corresponding separation region for a modifier concentration of c_F^{mod} 0.02 in the desorbent [region (b)]. Due to the constraints given by Eqs. (50) and (51) this region is much smaller than region (a), which was determined without

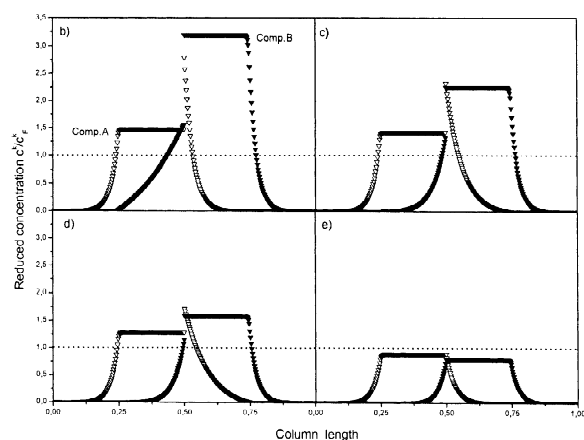


Fig. 11. Internal concentration profiles for the four selected points marked as crosses in the regions (b)–(e) shown in Fig. 10. All relevant parameters are summarized in Table 4.

Table 4

Parameters and results obtained for the four points marked in Fig. 10 as crosses; the corresponding internal concentration profiles are shown in Fig. 11

	Point 1, region (e)	Point 2, region (d)	Point 3, region (c)	Point 4, region (b)
c_F^{mod}	0.25	0.1	0.05	0.02
c_D^{mod}	0.25	0.25	0.25	0.25
c_{I-II}^{mod}	0.25	0.1834	0.1275	0.662
c_{III-IV}^{mod}	0.25	0.331	0.752	0.323
K_{I-II}^A	2	2.72	3.92	7.55
$K_{I,II}^B$	4	5.45	7.84	15.1
K_{III-IV}^A	2	3.75	6.64	15.44
K_{III-IV}^B	4	7.51	13.29	30.88
m_I	4.4	5.99	8.62	16.61
m_{II}	2.16	2.78	4.09	8.18
m_{III}	3.63	7.01	12.57	30.52
m_{IV}	1.82	3.41	6.04	14.03
\dot{V}_F^a	1.47	4.23	8.48	22.34
\dot{V}_E^a	2.23	3.18	4.53	8.43
\dot{V}_R^a	1.81	3.6	6.53	16.49
\dot{V}_D^a	2.58	2.58	2.58	2.58
Pur _R	0.999	0.999	0.999	0.989
Pur _E	0.999	0.998	0.999	0.999
c_B^A/c_F^A	0.81	1.16	1.29	1.35
c_E^B/c_F^B	0.65	1.32	1.87	2.62

^a $\dot{V}_S = 1$.

constraints. An increase of the modifier content in the feed obviously shifts the region to lower $m_{II} - m_{III}$ values [regions (b)–(e)]. Fig. 11 shows, for the four points selected in Fig. 10, the corresponding internal concentration profiles calculated using Eqs. (21) and (22). The decrease of the concentration level of the separated components A and B for a decreasing difference between the two modifier concentrations (i.e. for a decreasing gradient effect) is obvious. This is further exemplified by Table 4 which summarises the relevant parameters characterising the simulations presented in Fig. 11. Most noteworthy is the significant enrichment which could be achieved under gradient conditions.

6. Conclusions

In this paper a simple stage model capable to simulate linear two-step gradient counter-current chromatography is suggested. To solve the underlying equations efficiently an algorithm based on the

Kremser equation has been developed. With this tool a large range of the relevant operating parameters can be analyzed. The model and the algorithm were tested successfully by comparing separation regions for limiting cases (large stage numbers and high purity) with the results of available analytical solutions. With the more general model developed in this work, influences of reduced stage numbers and purity requirements can be quantified. The algorithm can be easily extended to analyze more complex gradient regimes (for example to simulate a specific elution strength for each of the four zones) or to include other processes (like recycling loops, first order reactions or subsequent crystallization steps).

The results obtained prove that the studied two-step gradient counter-current process is versatile and powerful. Properly designed it may lead to significant solvent reductions and may deliver more concentrated product streams compared to the isocratic process.

7. Nomenclature

a	parameter in Eq. (44), (–)
b	parameter in Eq. (44), 1/[c], e.g. (1/g)
c	fluid phase concentration, e.g. (g/l)
K	Henry coefficient, (–)
K_o	parameter in Eq. (44), (–)
m	flow-rate ratio, Eq. (45), (–)
M	stage number
N	overall stage number, (–)
Pur	purity, (–)
q	adsorbed phase concentration, e.g. (g/l)
\dot{V}	volumetric fluid phase flow-rate, (l/s)
\dot{V}_s	volumetric solid-phase flow-rate, (l/s)
x	fluid phase concentration, see Table 1, e.g. (g/l)

Greek letters

α	defined in Eq. (43), (–)
β	defined in Eq. (43), (–)
γ	factor in Eq. (21), (–)
η	factor in Eq. (22), (–)
χ	flow-rate ratio, defined in Eq. (11), (–)

φ safety factor, Eq. (50), (–)

Subscripts and superscripts

A	less retained component
Ab	referring in Table 3 to Abel et al. [15]
B	more retained component
D	desorbent
E	extract
ext	external
F	feed
i	zone index
ii	index for gradient steps, ($ii = I-II$ or $III-IV$)
j	stage index
k	component index
mod	modifier
port	raffinate (R) or extract (E)
R	raffinate

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