Multiple dual mode counter-current chromatography with variable duration of alternating phase elution steps

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ABSTRACT

The multiple dual mode (MDM) counter-current chromatography separation processes consist of a succession of two isocratic counter-current steps and are characterized by the shuttle (forward and back) transport of the sample in chromatographic columns. In this paper, the improved MDM method based on variable duration of alternating phase elution steps has been developed and validated. The MDM separation processes with variable duration of phase elution steps are analyzed. Basing on the cell model, analytical solutions are developed for impulse and non-impulse sample loading at the beginning of the column. Using the analytical solutions, a calculation program is presented to facilitate the simulation of MDM with variable duration of phase elution steps, which can be used to select optimal process conditions for the separation of a given feed mixture. Two options of the MDM separation are analyzed: 1 – with one-step solute elution: the separation is conducted so, that the sample is transferred forward and back with upper and lower phases inside the column until the desired separation of the components is reached, and then each individual component elutes entirely within one step; 2 – with multi-step solute elution, when the fractions of individual components are collected in over several steps. It is demonstrated that proper selection of the duration of individual cycles (phase flow times) can greatly increase the separation efficiency of CCC columns. Experiments were carried out using model mixtures of compounds from the GUESSmix with solvent systems hexane/ethyl acetate/methanol/water. The experimental results are compared to the predictions of the theory. A good agreement between theory and experiment has been demonstrated.

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1. Introduction

As recently noted by Conway [1], counter-current chromatography (CCC) provides an elegant and simple separation technique, in which the high volume fraction of stationary phase greatly enhances resolution. However, in some cases it is difficult to attain high values of stationary phase retention and there is a need to improve the technique when compounds with similar or extremely different partition coefficients are to be separated.

The separation efficiency of CCC columns for a given two-phase solvent system can be improved in different ways: (i) by optimizing of operating parameters; (ii) by increasing the length of the column using multilayer coils connected in series; (iii) applying knew operation modes and schemes, such as dual CCC, multidimensional CCC and intermittent dual CCC (cyclic dual-mode).

In dual CCC, two solvent phases are simultaneously eluted at opposite ends of the column while the sample is injected at the middle part of it [2–5].

Multidimensional separations are performed through the coupling of two or more identical or different columns with identical or different separation mechanisms to transfer the special peaks from the first dimension to the second and other dimensions [6–12].

In cyclic dual-mode processes, the CCC separation consists of a succession of two isocratic counter-current steps and is carried out in series alternating between normal phase (the upper phase pumped as the mobile phase) and reversed phase (the lower phase pumped as the mobile phase) operation [13–21]. All the variety of the resulting possible elution modes differ only in sample loading conditions: (i) the single sample is injected at the beginning of the column or the CCC separation is carried out in semi-continuous regime, with periodic sample re-injection after each cycle [15]; (ii) the sample is introduced into the middle section of the column during a certain time; (iii) the sample is fed continuously and at a constant rate into the middle section of the column. The first methodology as a single inversion between the stationary and the
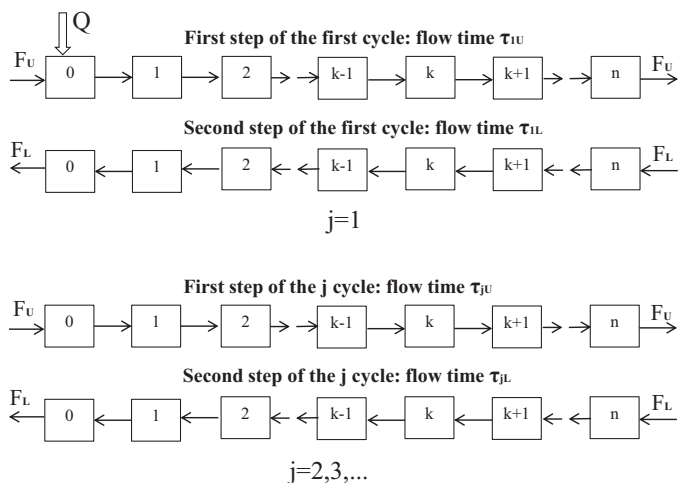
Fig. 1. Schematic diagram for mathematical model of multiple dual-mode counter-current chromatography with variable duration of phase elution steps.

mobile phase was described as dual-mode (DM) by Zhang et al. [13,14]. In a further development by Delannay et al. [15], it was extended to an iterative procedure made of a succession of dual-mode steps named multiple dual-mode (MDM). The same authors have proposed the sample re-injection between each of the dual-mode steps [15]. Rubio et al. [16] have applied MDM to the chiral CCC separations of two racemic mixtures.

The second method, called intermittent counter-current extraction (ICcE), was used by Hewitson et al. [17–19] to split a sample into two groups of compounds or concentrate a target compound inside the column. The continuous feed of the sample into the middle section of the column was applied by Hopmann and Minceva [20] to perform continuous separation in a unit consisting of two hydrostatic centrifugal columns and called sequential centrifugal partition chromatography (sCPC). It was also applied by Peng et al. [21] in analytical and preparative high-performance counter-current chromatography (HPCCC) and called intermittent counter-current extraction (ICcE). It should be noted that the methods with the continuous feed of the sample into the column actually represent one of the options of controlled-cycle counter-current extraction [22] and in contrast to the chromatography separations (the processes with short sample loading time) are rather related to the steady-state (or quasi-steady-state) extraction processes [23,24].

A distinctive feature of the above listed cyclic CCC separations is a shuttle (forward and back) movement of the sample in chromatographic columns. The idea of MDM method most clearly was presented by Yang, Aisa, Ito [25] and Mekaoui and Berthod [26]. According to this method, each phase elutes alternately through the opposite ends of the separation column at a given constant interval and flow rate. The flow is repeatedly switched back and forth to retain the two solutes inside the column until the two peaks are separated [25]. In [25] a mathematical model was developed to predict retention time of the solutes. The model is based on the general chromatographic retention equation to determine the rate at which the peak of a solute in the lower and upper mobile phase moves forward and backward through the column. The drawback of this approach is that it does not take into account the broadening of the peak as it moves through the column. In the work [26], the theoretical approach for the MDM method was developed taking in account the broadening of the solute peaks inside the CCC column by using the peak variance, and assuming Gaussian distribution.

The shuttle movement of the sample increases its residence time (the retention) in the column, which actually corresponds to an increase in length of the column. From this standpoint, it is desirable to use the full length of the column in each cycle. To retain a solute or group of solutes in the column for a specified number of cycles of alternating phase movements, it is necessary to reduce cycle times during the transition from one cycle to the next one.

For comparison of different variants of the process and choosing the best option to solve a particular separation problem, it is desirable to have an appropriate MDM theory. This paper is devoted to the further development of the theory for MDM with sample loading at the beginning of the column.

In this study, the mathematical description of the MDM method with sample loading at the beginning of the column and varying from cycle to cycle phase flow durations is presented. Experiments were carried out on the controlled-cycle pulsed liquid–liquid chromatography device [27] using model mixtures of compounds from the GUESSmix [28] with solvent systems hexane/ethyl acetate/methanol/water (HEMWat). The experimental results are compared to the predictions of the theory. The agreement between theory and experiment appears to be acceptable.

2. Theory

We will consider linear chromatography to develop analytical solutions and build on the cell model [19,23,29–31], which takes into account the influence of axial mixing and interphase mass transfer on the separation of solutes in a chromatographic column.

2.1. Mathematical model of multiple dual-mode counter-current chromatography with variable duration of phase elution steps

As mentioned above, an MDM separation process consists of a succession of counter-current dual-mode cycles. Each cycle comprises two isocratic steps (Fig. 1): the first step – the upper phase pumped as the mobile phase (usually normal phase and ascending mode operation); the second step – the lower phase pumped as the mobile phase (reversed phase and descending mode operation).

The process starts in normal phase with the upper phase mobile. According to Fig. 1, the mass balance equations of the equilibrium cell model as applied to a dual-mode cycle of the MDM process have the following form:

For the first step:

$$\frac{V_U}{N}\frac{dx_0}{d\tau} + \frac{V_L}{N}\frac{dy_0}{d\tau} = \frac{(V_U + K_D V_L)}{N}\frac{dx_0}{d\tau} = -F_U x_0 \tag{1}$$

$$\frac{V_U}{N}\frac{dx_k}{d\tau} + \frac{V_L}{N}\frac{dy_k}{d\tau} = \frac{(V_U + K_D V_L)}{N}\frac{dx_k}{d\tau} = F_U x_{k-1} - F_U x_k;$$
$$k = 1, 2, \ldots, n \tag{2}$$

For the second step:

$$\frac{V_U}{N}\frac{dx_k}{d\tau} + \frac{V_L}{N}\frac{dy_k}{d\tau} = \frac{(V_U/K_D + V_L)}{N}\frac{dy_k}{d\tau} = F_L y_{k+1} - F_L y_k;$$
$$k = 0, 1, 2, \ldots, n-1 \tag{3}$$

$$\frac{V_U}{N}\frac{dx_n}{d\tau} + \frac{V_L}{N}\frac{dy_n}{d\tau} = \frac{(V_U/K_D + V_L)}{N}\frac{dy_n}{d\tau} = -F_L y_n \tag{4}$$

where F_U and F_L are the volumetric flow rates of upper and lower phases, respectively;

$$K_D = \frac{\text{eq.LP-concentration}}{\text{eq.UP-concentration}}$$

$$= \frac{y_{eq}}{x_{eq}} - \text{ratio of equilibrium phase concentrations};$$

$N = n + 1$. is the total number of equilibrium cells in the column; V_U and V_L are the volumes of upper and lower phases in the column,