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REVIEW

SYSTEMATIC APPROACH TO COLUMN SWITCHING

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1. INTRODUCTION

Modern liquid chromatography becomes more attractive and more powerful if the number of separation columns is increased. Usually a liquid chromatographic system contains a simple flow-through sequence. If this sequence is branched and switching devices are used to interface individual columns to a chromatographic network[1–3], liquid chromatography becomes a versatile and powerful separation system.

Column switching leads to an on-line approach to sequential column chromatography. A fraction of the effluent from a primary column is selectively transferred to a secondary column for further separation. Highly selective separations are achieved by changing the operating basis by using different transfer techniques and/

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or switching functions or by changing the chromatographic modes of separation during the overall process.

The chromatographic modes usually refer to the separation mechanism which the chromatographer intends to provide. The chromatographic mode or separation mechanism depends on the overall interactive relationships between the analyte, the mobile phase and the stationary phase. Neither the chromatographic modes, *e.g.*, multi-dimensional, solvent switching or post-column acceleration, nor the objectives of the chromatographic modes applied, *e.g.*, trace enrichment, front cut or heart cut, are well suited to describe column switching networks. The operating bases of the transfer techniques and the switching functions used throughout the network are unrelated to the chromatographic modes and therefore best suited to define clearly the column switching network.

It is the aim of this paper to help disentangle related or equivalent terms used to describe column switching techniques by well defined transfer techniques and switching functions. By this systematic approach, appropriate column networks may be set up in a easily surveyed manner.

2. DEFINITION OF THE TERM COLUMN SWITCHING

The term column switching is used in modern liquid chromatography for different operating modes without a strictly defined sense. Synonymous expressions such as "multiple column chromatography", "sequential chromatography", "multi-channel chromatography", "split chromatography", "coupled column chromatography", "isomodal, bi- or heteromodal chromatography", etc., are used for column switching, but with different objectives for chromatographic separations.

The term column switching[4] includes in the widest sense all techniques by which the direction of flow of the mobile phase is changed by valves, so the effluent from a primary column is passed to a secondary column for a defined period of time. The use of valves means that the chromatographic system involves not one, but a number of columns forming a network. Switching within this network may be effected manually or by automated controllers.

The objectives of column switching are (1) to increase the chromatographic resolution and selectivity; (2) to enrich trace amounts of sample; (3) to protect sensitive detectors (*e.g.*, electrochemical detectors) from contamination by coextractives; (4) to prevent destabilization of the chromatographic equilibrium of the column by coextractives; and (5) to achieve further objectives or a combination of several objectives within one chromatographic network.

Throughout this paper "primary column" indicates the column from which the analyte fractions are transferred to the following "secondary column". Primary and secondary eluents are the respective mobile phases used for elution of the corresponding columns.

3. TRANSFER TECHNIQUES AND SWITCHING FUNCTIONS

Four basic techniques are used to transfer a sample fraction from primary to secondary columns. Depending on the direction of flow of the mobile phase during the transfer period, a direct or a reversed flow direction can be distinguished. The

direction of flow and the origin of the transfer mobile phase, whether it is used as a primary or a secondary column eluent, are thereafter the parameters used to characterize the transfer techniques.

In addition to the different transfer techniques there are several switching functions, which are used to optimize chromatographic parameters. Commonly used column switching functions are column backflusing, column selection and recycling chromatography.

3.1. Direct transfer technique

Fig. 1a shows the switching valve arranged in the direct transfer technique. The primary mobile phase enters the valve (IN) and flushes the column. The moment the analyte starts to elute the column, the switching valve is rotated into the transfer position (ON) (Fig. 1b). The analyte fraction separated is directed through the OUT port with the primary mobile phase on to the secondary column. After the analyte fraction of interest has eluted completely from the primary column, the valve is rotated back and the secondary mobile phase (PUMP port) starts to elute the analyte from the secondary column. No reconditioning of the primary column is needed as the column is always flushed with the same mobile phase.

3.2. Indirect transfer technique

Fig. 2a shows the switching valve arranged for executing the indirect transfer technique. The primary mobile phase enters the valve through the IN port and flushes the column. The primary mobile phase separates the analytes, but the analytes of interest do not elute from the column. After rotating the switching valve (Fig. 2b) into the transfer position (ON), the secondary mobile phase with a higher elution power than the primary mobile phase is directed on to the primary column. The analytes now elute from the column and are transferred on to the secondary column through the OUT port. After elution of the analytes is completed, the valve is rotated back

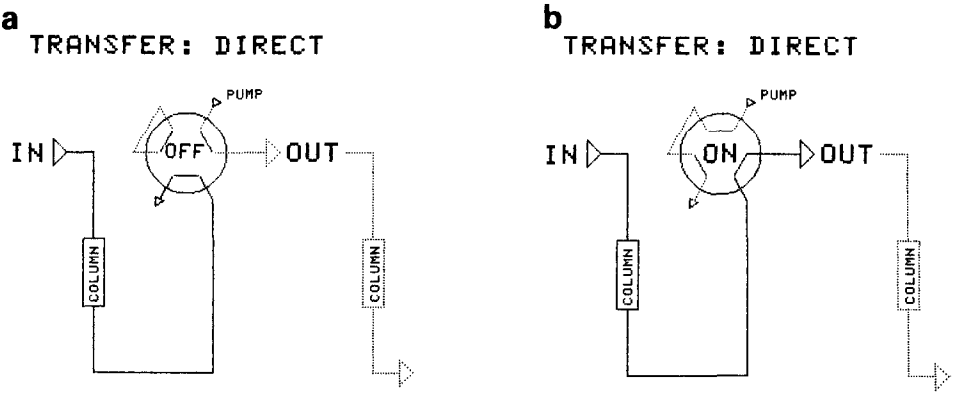

Fig. 1. (a) Elution of primary column. (b) Transfer on to the secondary column with primary eluent. The following notations are used in all figures: IN = primary eluent entrance of the primary column, flow from previous system part (*e.g.*, injection valve); OUT = eluent exit, flow on to the secondary column; PUMP = eluent pump of the secondary column; OFF = valve in the standby position; ON = valve in the switching position; straight line shows the actual flow, dotted lines are flow lines of the secondary column or bypass flow lines.

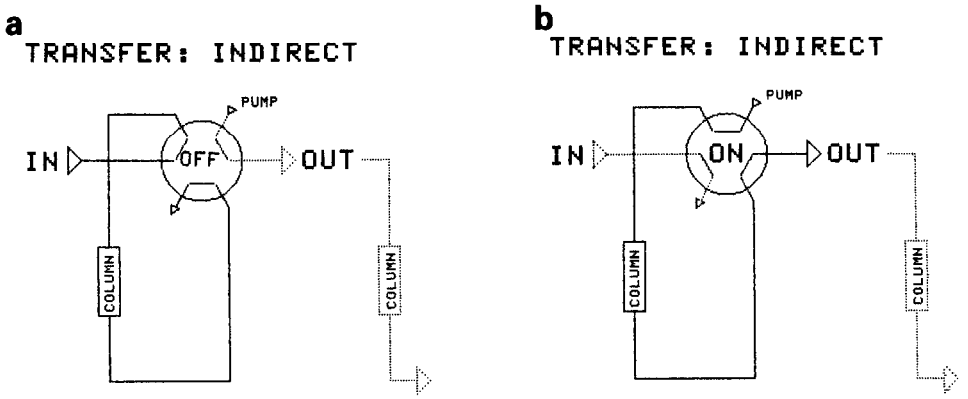

Fig. 2. (a) Elution of the primary column. (b) Transfer on to the secondary column with the secondary eluent.

(position OFF, Fig. 2a). The secondary mobile phase now separates the analyte fraction on the secondary column, while the primary column is reconditioned with the primary mobile phase.

3.3. Reversed transfer technique

Fig. 3a shows the basic setup of a chromatographic network for reversed transfer of the analytes on to the secondary column. The analytes are not necessarily separated with the primary mobile phase on the primary column. The fraction of interest does not elute from the column. After rotating the switching valve into the transfer position ON (Fig. 3b) the secondary mobile phase, which is an eluent equal to or stronger than the primary mobile phase, is delivered through the pump entrance and transfers the fraction of the analyte of interest by reversing the flow direction of the primary column through the OUT port on to the secondary column. When the transfer of the analyte is completed, the switching valve is rotated back (Fig. 3a). The

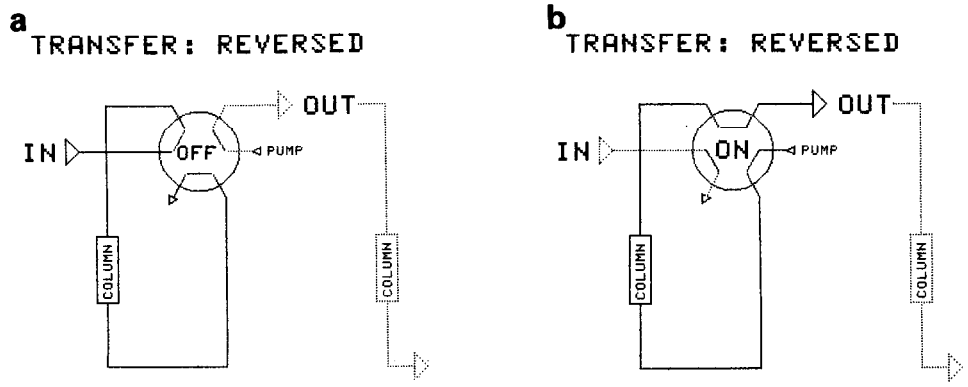

Fig. 3. (a) Elution of the primary column. (b) Transfer in reversed flow direction on to the secondary column with the secondary eluent.

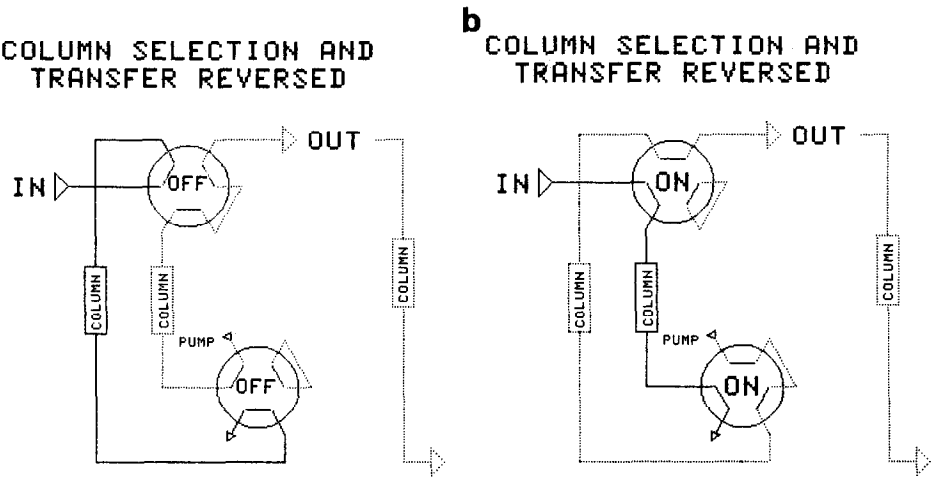

Fig. 4. (a) Elution of the left-hand primary column and transfer of the right-hand primary column in reversed flow direction on to the secondary column with the secondary eluent. (b) Elution of the right-hand primary column and transfer of the left-hand primary column in reversed flow direction on to the secondary column with the secondary eluent.

secondary mobile phase now separates the analyte fraction on the secondary column, while the primary column is reconditioned.

Fig. 4. shows a special setup for reversed transfer which uses two primary columns alternately. The left column is connected in-line to the sampling eluent stream (IN) (Fig. 4a). The right primary column is flushed with the eluent of the secondary column in the reversed transfer technique and the analytes are separated on the secondary column. After rotating both valves into the ON position (Fig. 4b) the secondary eluent flows in a reverse direction through the left column and the right column is loaded with the analyte of the next sample[5].

3.4. Loop transfer

Fig. 5a shows a modification of the direct transfer technique. The primary and secondary columns are not connected on-line during the transfer period. This transfer technique avoids excessive pressure on the primary column during the transfer period. The effluent from the primary column is collected in a loop and re-injected into the secondary column (Fig. 5b). A disadvantage of the loop transfer technique is that the volume of the transfer fraction is given by the loop volume so the components of interest to be transferred must elute from the primary column in a sufficiently high concentration to allow the transfer of all or at least the major part of the sample fraction.

The loop transfer technique is principally possible as a modification of each basic transfer technique. The indirect or reversed transfer techniques necessitate an additional loop valve.

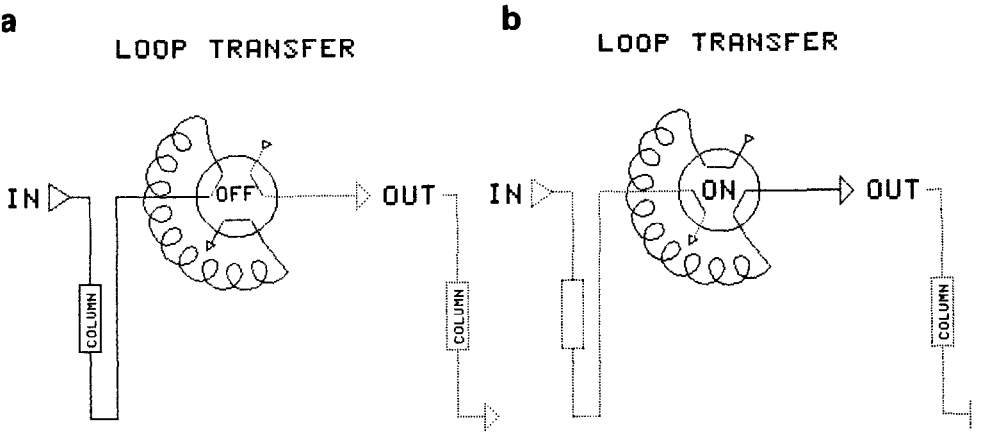

Fig. 5. (a) Elution of the primary column through the transfer loop. (b) Re-injection of the loop volume on to the secondary column with the secondary eluent.

3.5. Column backflushing

The effluent from the primary column is normally vented to waste for bypassing the secondary column and for preventing its contamination by early or late eluting components. Backflushing the primary column removes samples components that are strongly[1] retained. After the fraction of interest has eluted from the primary column and has been transferred for further separation on to the secondary column, this technique reverses the flow of the primary column to waste (Fig. 6a and b).

A more powerful cleaning eluent may replace the mobile phase (Fig. 7a and b). Backflushing speeds up the analysis of complex mixtures without the use of gradient elution.

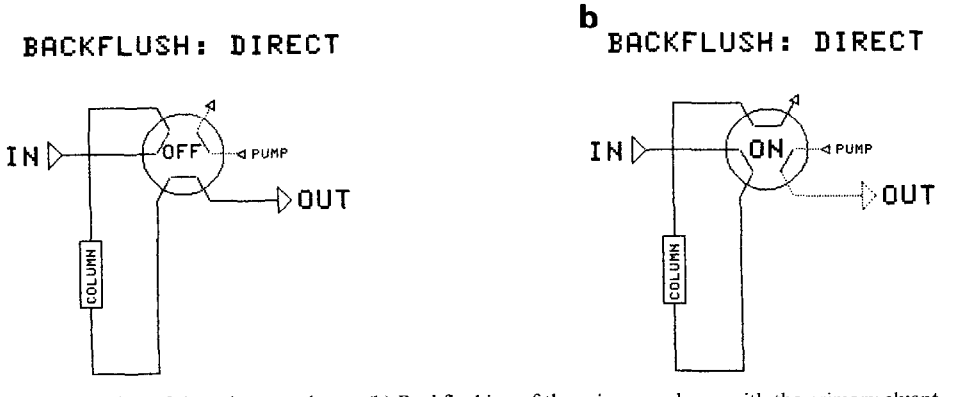

Fig. 6. (a) Elution of the primary column. (b) Backflushing of the primary column with the primary eluent waste.

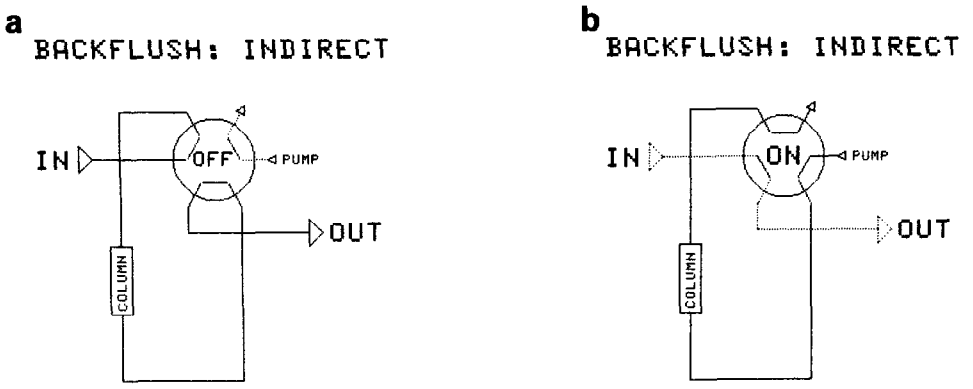

Fig. 7. (a) Elution of the primary column. (b) Backflushing of the primary column with a rinsing eluent to waste. PUMP = rinsing eluent pump.

3.6. Column selection

Column switching systems[6–8], designed to reduce long analysis times, use two or more (different) columns to perform the separation of analytes with very different capacities rather than a single, long column. Late eluting components are directed after the primary (short) column to the detector, whereas the fast eluting components are separated on the secondary (long) column before they are detected (Figs. 8–10).

Usually all columns are run with the same eluent (Fig. 8a). During the elution of components of high capacity from the primary column (Fig. 8b), the secondary column is in the standby position with no eluent flow. Normally no band broadening occurs once the flow of the column is restored, as longitudinal diffusion is very slow in packed columns.

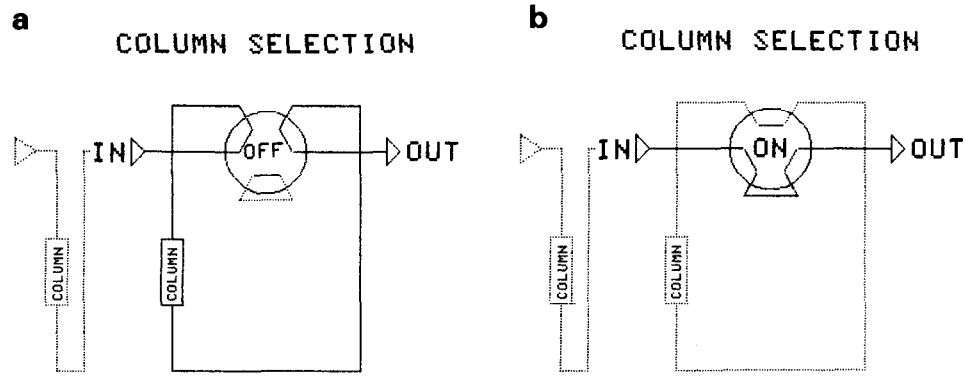

Fig. 8. (a) Elution of both columns with the same eluent. (b) The second column with the early eluting components in the bypass position.

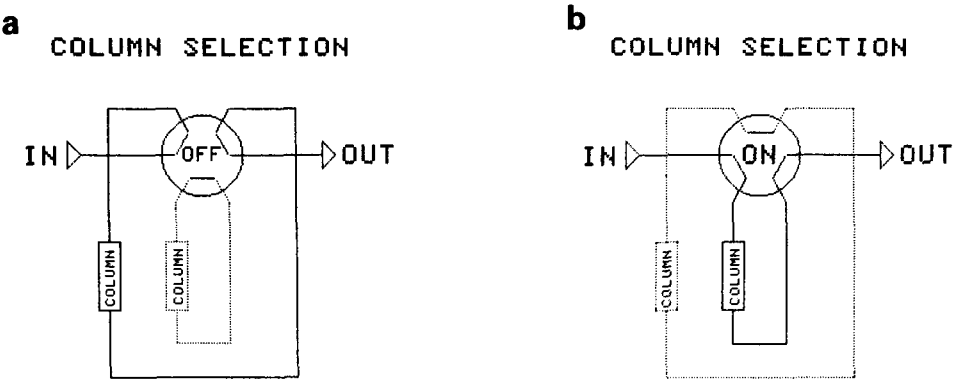

Fig. 9. Either column is to be switched into the eluent stream.

Column selection offers an alternative approach to chromatographic adjustment by solvent switching or gradient elution and it avoids the problem of slow column equilibration.

Fig. 9a and b show a system for selecting two different columns run with the same mobile phase. This arrangement is well suited to select between two different column lengths.

3.7. Recycling chromatography

Recycling chromatographic systems use the same column by re-injecting a portion of the chromatographic effluent from the column. The repeated use of the same column increases the number of theoretical plates. Recycling can be carried out by using an alternative column principle (Fig. 10), where two columns are used in sequence[9,10].

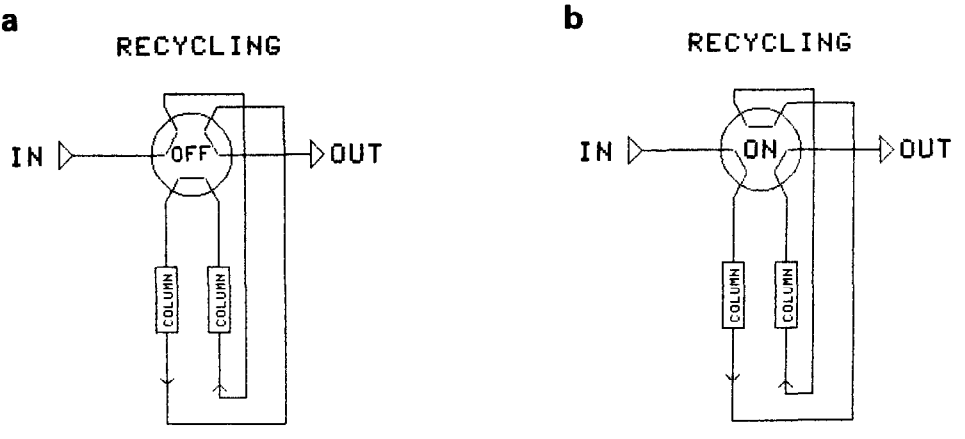

Fig. 10. The sequence of columns is changed periodically, which increases the total column length. (a) Flow from the left column is directed to the right column. (b) Flow of the right column is redirected to the left column.

The recycling technique offers, in comparison with the column selection technique, the possibility of increasing the column length by repeated use of the same columns (Fig. 10a and b).

4. TRANSFER TECHNIQUES AND THE CHROMATOGRAPHIC MODES

4.1. Change of the chromatographic modes by column switching

Highly selective chromatographic separations are achieved by changing the mode of separation during the chromatographic procedure. In particular, mode control or mode sequencing in chromatography involves several changes of the composition of the mobile phase and/or stationary phase. Systematic changes of mode during the chromatographic separation process contribute to a cooperative unlimited and overall increase in the separation capability and selectivity of the system[1,11–15]. These sequential changes of the chromatographic modes are known as multi-dimensional column chromatography, stationary phase programming and selectivity switching, among others.

The term "multi-dimensional" currently encompasses other on-line switching modes, such as backflushing, detector or column bypassing, system setups of two or more columns in parallel, etc., which are switching functions and are not based on a multi-dimensional chromatographic mode.

4.2. Fractional transfers

Wide or narrow cuts of the chromatographic effluents from primary columns are transferred to the secondary column by flow switching and the mobile phase flow is thereby diverted or reversed. The fraction of interest to be transferred on to the secondary column may elute at the front (first eluting zone) or in the middle of the chromatographic effluent (heart) or at the end (last eluting part) of the chromatogram of the primary column. Obviously always one or more fractions or zones of the whole chromatographic effluent are transferred from the primary on to the secondary column. The notations used to specify these fractional parts[16,17] of the chromatograms or to name the switching technique according to the transfer fraction as a front, heart or end cut express neither the column to column transfer technique nor the chromatographic objective intended to be achieved by the switching technique. Therefore, the transfer techniques presented in Section 3 should be used exclusively to describe a column switching system.

4.3. Peak compression after band spreading

The band broadening during chromatographic separations based on diffusion effects necessitates the transfer of wide fractions of the effluent from the primary to the secondary column[7,18]. The separation and sensitivity of the chromatographic system may be improved if sample dilution is minimized throughout the analysis. This involves reconcentration of the transferred fractions in each successive step. The elution strength of the mobile phase and the retention capability of the stationary phase should increase to reconcentrate the analyte at the top of the secondary column to reduce band broadening. This reconcentration effect is referred to as on-column concentration. Reconcentration at the top of the secondary column is also increased by diluting the effluent from the primary column with a solvent of low elution strength before directing the flow on to the secondary column.

4.4. Precolumns and guard columns

Precolumns in the widest sense in the literature are used as primary columns. They are tailored for special purposes (trace enrichment, sample cleanup, etc.) and normally they are not intended to separate samples by chromatographic means. Guard columns are short columns connected in-line with the analytical column. They are strictly used to prevent the analytical column from rapid deterioration. The primary column of column switching systems acts as a guard column for all secondary columns.

5. APPLICATIONS OF COLUMN SWITCHING

Analytical samples are often so complex that one or several of the target components must be determined within a matrix of a very large number of other components that are present at higher or lower concentrations. Multi-step methods are necessary with several purification steps before the final chromatographic determination. Column switching systems should permit the multi-step methods to be transformed into single-step procedures by on-line purification. These systems allow firstly the injection of a large volume of sample to increase the sensitivity and secondly the optimization of the separation by gradual adjustment of the resolution parameters.

Probably the most important applications of column switching are trace enrichment, sample cleanup, group separation and chromatographic adjustment.

5.1. Trace enrichment

The analysis of a single or a few components in trace amounts in biological matrices is a general problem. Trace enrichment or preconcentration by on-line chromatographic techniques are based on the fact that the components will be retained in a narrow zone on the top of the column when a large volume of sample is pumped through the column[19–21]. Good reproducibility is obtained if the column is not overloaded and if the capacity of the column is not exceeded. Overloading can be overcome by diluting the sample before injection. If trace enrichment has to be effected for less strongly adsorbed components, the sample volumes must be smaller or the column volume must be increased to prevent breakthrough. Trace enrichment is performed when relatively non-polar components from aqueous solutions are injected on to a reversed-phase column. Similar phenomena can be exploited with adsorption chromatographic systems using suitable solvent polarities. Subsequent elution with a stronger eluent by indirect transfer (Fig. 2) or by reversed transfer (Figs. 3 and 4) will reconcentrate the sample zone and start the separation procedure on the secondary column. Unfortunately, trace enrichment also concentrates sample components other than the analyte. As a consequence, cleanup may well be insufficient and the subsequent separation of the components of interest from interfering substances may necessitate further on-line cleanup steps.

5.2. Sample cleanup

The principle of on-line sample cleanup is to analyse one fraction and to discard all others[2,21,22]. The degree of improvement of a separation is based on the reduction of the amount of interfering components relative to the amount of analyte. This objective is achieved by selecting the size of the fraction to be transferred from the

primary column to the secondary column in such a way that the transferred fraction contains the analyte and as little as possible of the overlapping interferences. By on-line multi-step fractionation (Fig. 1, direct transfer; Fig. 5, loop transfer; or Fig. 8, column selection), the analyte is gradually enriched relative to the interfering components. Therefore, the degree of separation is improved compared with a single-step operation with the same chromatographic resolution.

5.3. Group separation

In a preliminary fractionation the sample is divided into groups of components sharing some chromatographic characteristics defined by the fractionation method. This chromatographic fractionation selects groups of components with, *e.g.*, similar molecular size[16,18,23] or similar retention characteristics (anion, cation, etc.)[24,25], reflecting a comparable type and strength of interaction with the stationary phase. The choice of a primary chromatographic system, which selects some characteristics unique to the components of analytical interest, reduces the number of components to be transferred on to the secondary column. This results in fewer peaks and increased resolution of the secondary analytical system compared with the direct separation of the whole sample.

Nielen *et al.*[25] used small columns packed with different stationary phases for the on-line group separation and trace enrichment of industrial waste water. They divided the sample into three main groups, a fraction containing non-polar components adsorbed on C_{18} stationary phase, a fraction of medium polarity components adsorbed on PRP-1 (a polystyrene–divinylbenzene phase) and a fraction of polar bases adsorbed on cation-exchange phases. Each fraction was subsequently chromatographed on a C_{18} reversed-phase analytical column using a column switching network built up according to the column selection mode in Fig. 8.

Gel permeation or size exclusion chromatography[16,18,23] selects only those components with comparable molecular sizes. For complex samples a narrow molecular size fraction contains many components with a wide variety of functional groups. These components elute over a wide capacity range in the secondary column. Ogan and Katz[23] described a multi-function system for the determination of polycyclic aromatic hydrocarbons in coal liquid and oils by using the loop transfer technique (Fig. 5) from or on to gel permeation or size exclusion columns.

5.4. Chromatographic adjustment

Selection of a suitable column length for each analyte of the sample or selection of a suitable stationary phase for each group of analytes by the column selection technique are two of various possibilities of the adjustment of chromatographic parameters (Figs. 8–10).

Backflushing of the primary column offers another possibility of adjusting the run time, as late eluting interferents are backflushed to waste, while the analytes are separated on the secondary column (Figs. 6 and 7).

Chromatographic adjustment by column switching offers an effective alternative to solvent adjustment by gradient elution or solvent switching followed by reconditioning of the column.

6. COLUMN NETWORKS

6.1. Example of a two-valve network (three columns)

Fig. 11a–e show a two switching valve network with reversed transfer from the first to the second column and with direct transfer from the second to the third column. This configuration corresponds to a combination of Figs. 3 and 1. The network is used for trace enrichment and cleanup on the first column (Fig. 11a). The first column is washed with mobile phase. After this wash period the valve "transfer reversed" is rotated to position ON (Fig. 11b) and the flow of the first column is reversed and directed to the second column. The analyte is transferred in the reverse flow direction by the stronger eluent of the second column. The original position of the valve (Fig. 11c) is restored (OFF position). The first column is reconditioned, while the analyte is separated on the second column. When the analyte fraction of interest starts to elute from the second column, the valve "transfer direct" is rotated to position ON (Fig. 11d). After the entire analyte fraction has eluted from the second column, the valve is reset (OFF position) and the separation on the third column starts (Fig. 11e).

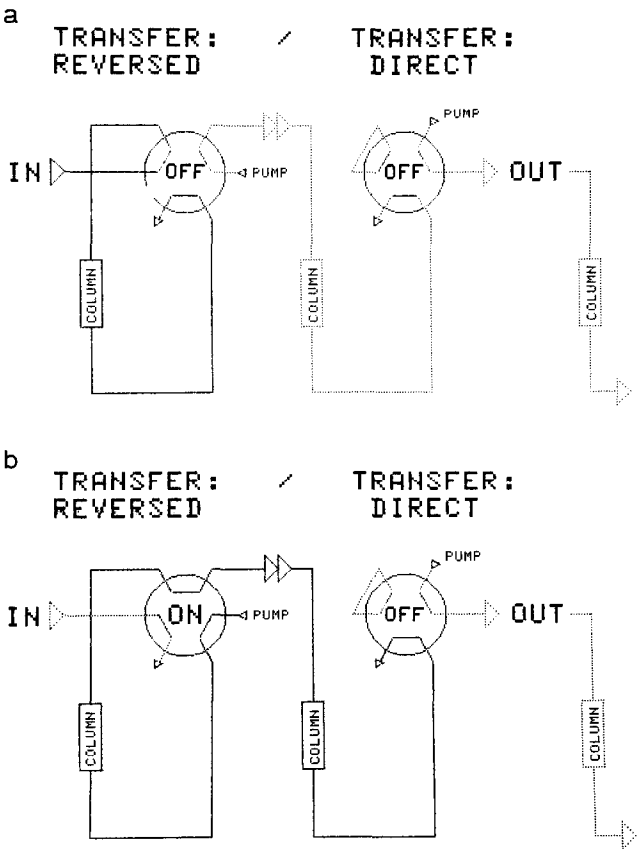

Fig. 11.

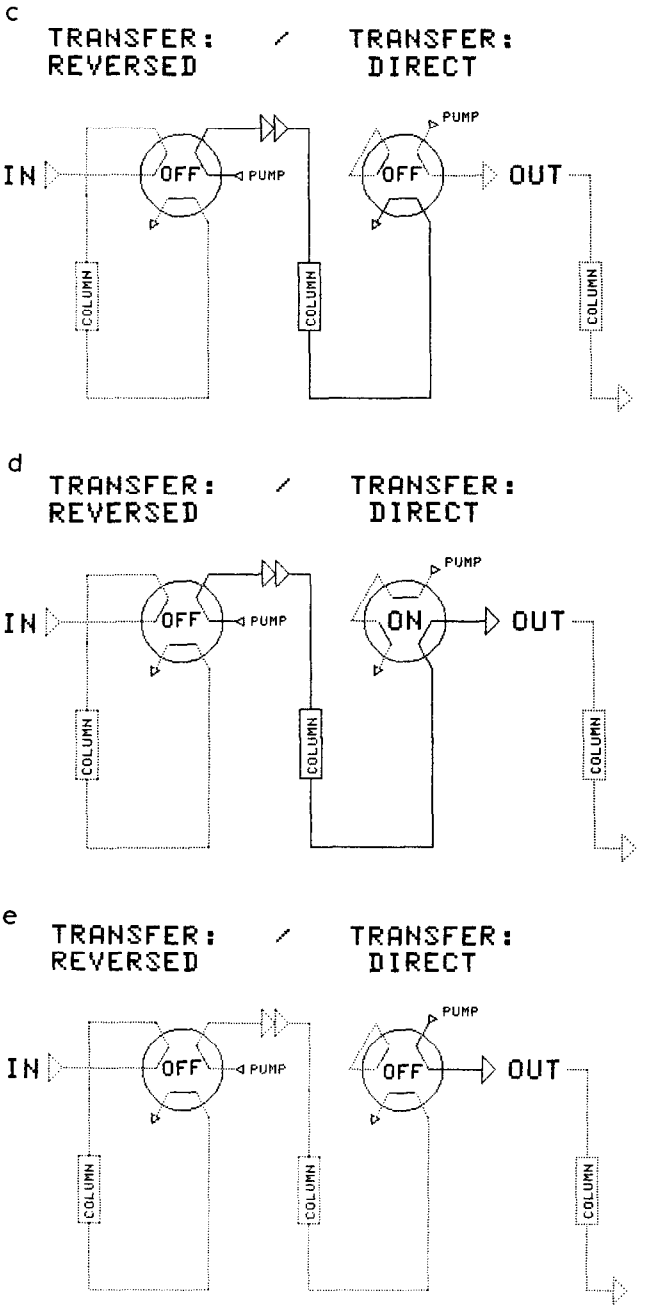

Fig. 11. Column network combination of reversed transfer (Fig. 3) and direct transfer (Fig. 2); column I = left, column II = middle and column III = right column. (a) Elution of the primary column I. (b) Transfer by reversed flow direction on to the secondary column II with the eluent from column II. (c) Elution of column II; the column now becomes the primary column for the next transfer. (d) Transfer of the primary column II on to the secondary column III with the eluent from column II. (e) Elution of the secondary column III.

6.2. Networks with column backflushing capability

Backflushing capability is included in any system configuration when the original column is replaced by the backflushing configuration's IN and OUT ports, respectively. Figs. 12–14 show the direct, indirect and reversed transfer techniques with the additional backflushing valve. The dotted centre column shows the original position of the primary column. The dashed lines in Figs. 12–14 show the flow of the mobile phase for backflushing the primary column. In the direct transfer technique, the mobile phase used to elute and to transfer the analyte is also used to backflush the primary column. In the indirect and reversed transfer technique, a separate pump with normally a stronger solvent than the eluent is used to backflush the column.

7. CONCLUSION

The technique of transfer of effluent fractions governs the application of column switching. Four different column to column transfer techniques together with three additional switching functions meet the needs of most of the on-line chromatographic separation modes described in the literature such as trace enrichment, sample cleanup, chromatographic fractionation and group separation.

By combining the valve configurations described for the specified transfer techniques, the setup of complex column networks is simplified with standard six-port high-pressure switching valves. The networks are described clearly by the transfer technique from column to column and/or the switching function but not by the chromatographic effect achieved by the system.

Special setups for liquid–gas chromatography transfer or chromatographic mode changes (adsorption to reversed or *vice versa*) are not considered in this paper.

8. SUMMARY

The term column switching in liquid chromatography is used if two or more columns are connected to form a network. The aim of column switching is to increase the chromatographic resolution and selectivity without losing sensitivity.

Many terms are used in the literature to characterize different column networks. Generally the resulting chromatographic effects are used to describe the switching system. Only rarely do authors define the technique used to achieve the transfer of a fraction of the eluent from one column to the next. This paper describes four basic techniques for transfer sample fractions: (1) direct transfer, (2) indirect transfer, (3) reversed transfer and (4) loop transfer. To optimize the chromatographic separation by column switching, additional commonly used switching functions are defined: (5) backflushing technique, (6) column selection or column bypass and (7) recycling chromatography. By linear combinations of different transfer techniques and/or switching functions, multifunctional column networks are designed in a simple way. They are used for trace enrichment, sample cleanup, chromatographic fractionation and chromatographic adjustments.

This paper is intended to provide a contribution to the standardization of nomenclature in column switching. Drawings of the particular column and switching valve arrangements are given together with examples of networks built up by combinations of transfer techniques and switching functions.

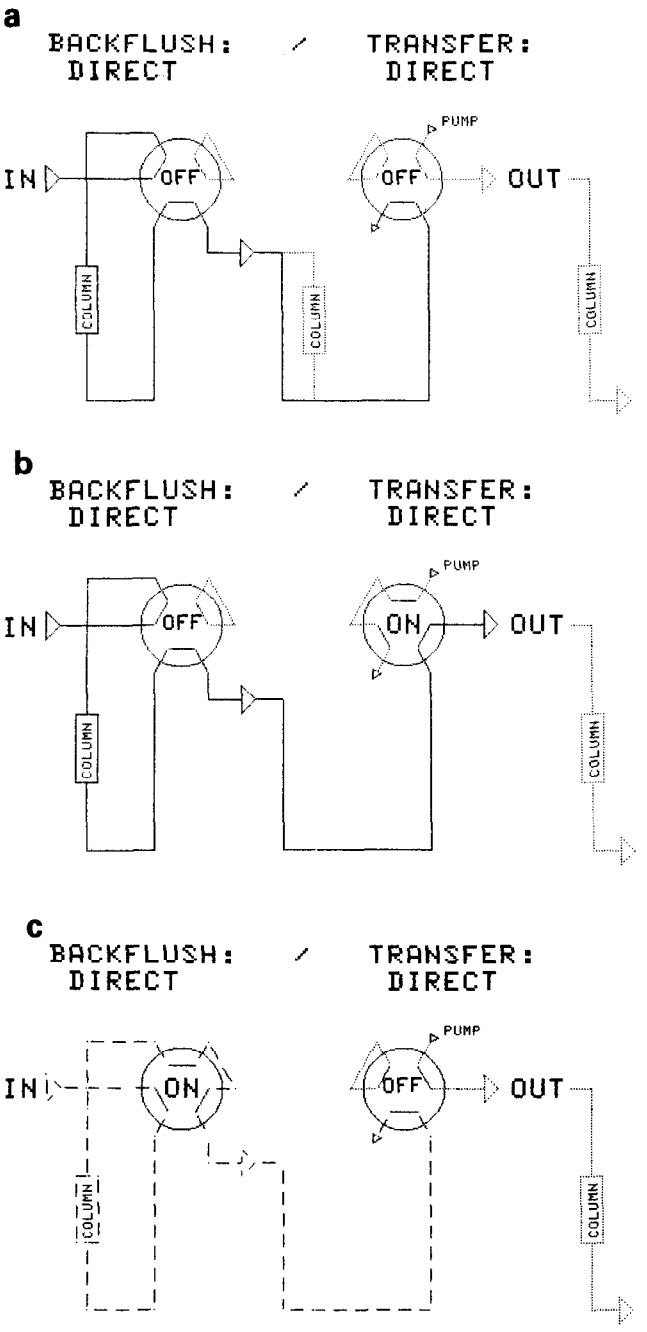

Fig. 12. Column network combination of direct backflushing of the primary column (Fig. 6) with direct transfer on to the secondary column (Fig. 1); dotted column (middle) shows the primary column position substituted by the backflushing valve. (a) Elution of the primary column. (b) Direct transfer on to the secondary column. (c) Broken line shows the backflushing flow of the primary eluent during elution of the secondary column with the secondary eluent.

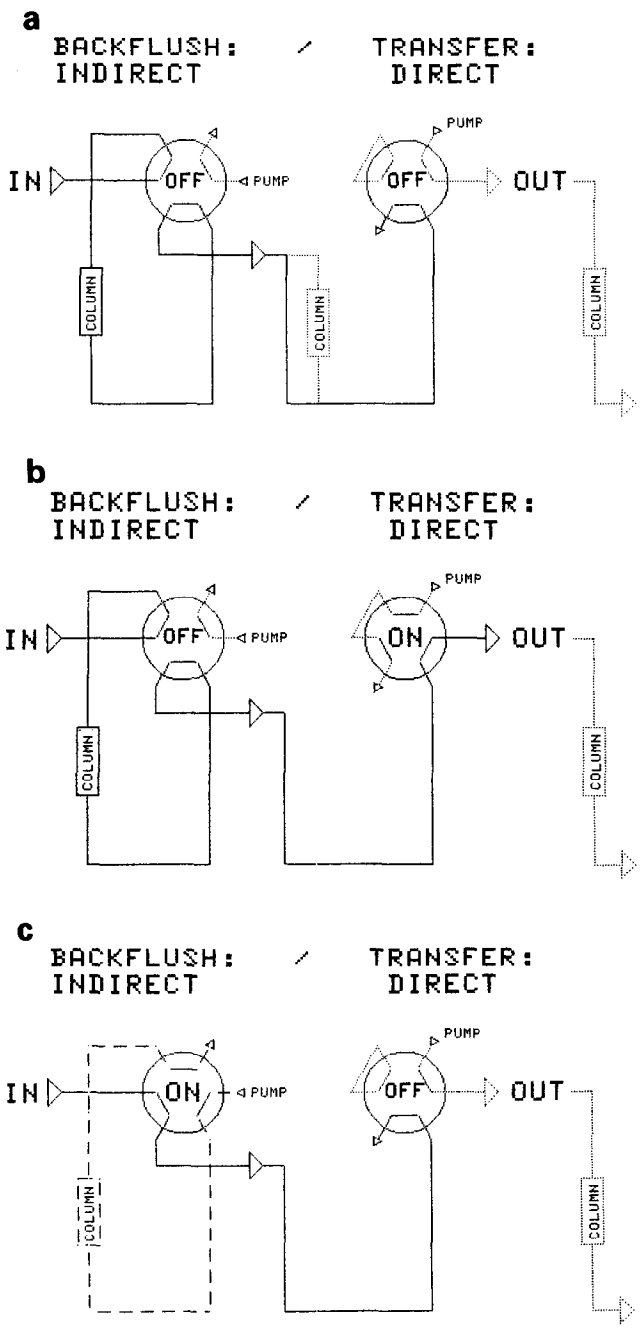

Fig. 13. Column network combination of indirect backflushing of the primary column (Fig. 7) with direct transfer on to the secondary column (Fig. 1); dotted column (middle) shows the primary column position substituted by the backflushing valve. (a) Elution of the primary column. (b) Direct transfer on to the secondary column. (c) Broken line shows the backflushing flow with a rinsing mobile phase not used for elution of the columns, during elution of the secondary column.

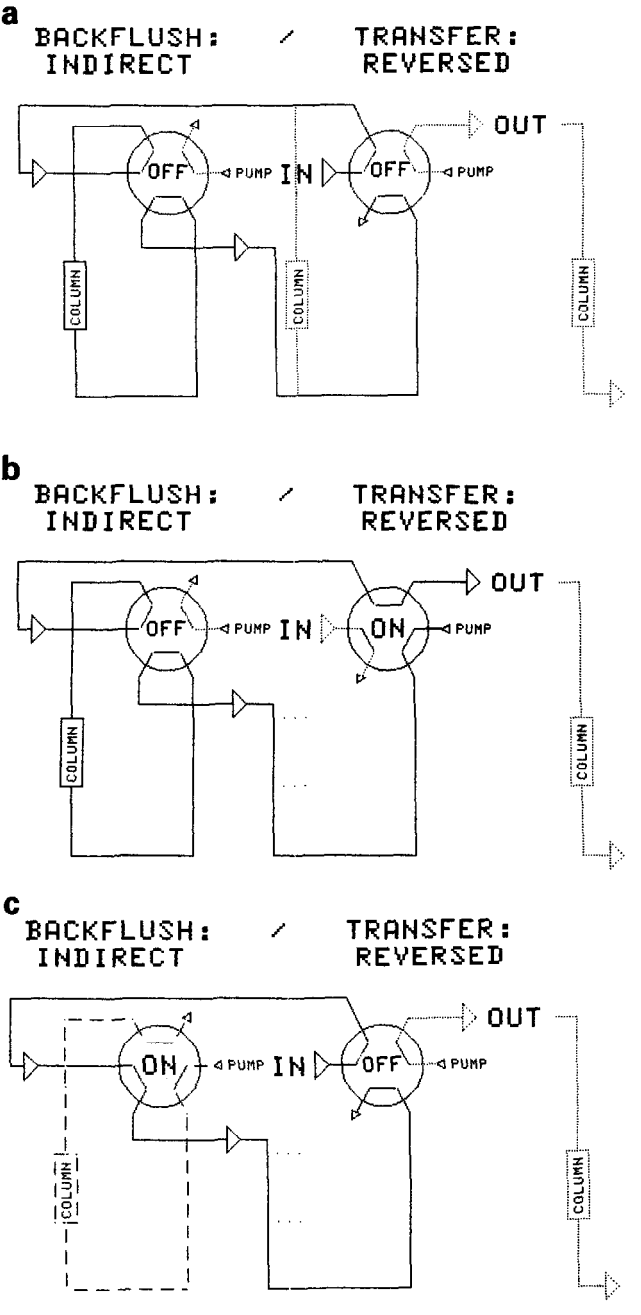

Fig. 14. Column network combination of indirect backflushing of the primary column (Fig. 7) with reversed transfer on to the secondary column (Fig. 3); dotted column (middle) shows the primary column position substituted by the backflushing valve. (a) Elution of the primary column. (b) Transfer by reversed flow direction of the primary column with the eluent from the secondary column. (c) Broken line shows the backflushing flow with a rinsing mobile phase not used for elution of the columns, during elution of secondary column.

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