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DYNAMICS OF ISOTACHOPHORETIC SEPARATION

I. COMPUTER SIMULATION

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SUMMARY

A simulation model formulated on an EAI 690 hybrid computer system is described. This model makes it possible to simulate with very good precision the dynamics not only of isotachophoretic, but also of any electrophoretic separation of the maximum number of four strong, uni–univalent electrolytes with a common counter ion.

INTRODUCTION

The solution of the dynamics of an isotachophoretic (electrophoretic) separation consists in a mathematical formulation of the problem and in the solution of the corresponding partial differential equations. A direct (analytical) solution of the whole set of these equations is impossible because of their complexity, even if the whole problem is formulated as an one-dimentional one (*i.e.*, the appropriate partial differential equations have only two independent variables, time and the distance from the origin). Hence the only possibility of solving this set of partial differential equations is to use a computer and to apply a suitable approximation method.

The general formulation of the mathematical description of the dynamics of an electrophoretic separation can be found in many papers, *e.g.*, refs. 1–3. However, attempts at a solution of even simplified systems of partial differential equations describing such dynamics are rare. The most complete computer models of this type have recently been described[4–8].

In our Department, modelling of the dynamics of zone electrophoresis was studied at the beginning of the 1970s using analog computers[9–11], assuming such a high concentration of the base electrolyte that the transport equation had to be solved idenpendently for each component. Even under these conditions it was found that the problem is soluble on a classical analog computer only for a limited number of points (a short time from the beginning of the separation). The solution of an isotachophoretic separation, when the equations must be solved simultaneously for all the substances, is even more demanding on the computer capacity. In view of the capacity of the MEDA SOT analog computer (at most 24 integrators) on which

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solution of this problem was attempted, it was possible to compute only the starting phase of the adjustment of the terminating electrolyte concentration, even when using the simplest model[12].

Further attempts to construct a computer model of the dynamics of the isotachophoretic separation were made in our Department using digital computers, where it was possible to include in the calculations the effect of diffusion and the concentration dependence of the mobilities (employing the Onsager and Fuoss electrolyte theory). After testing on a small MINSK 22 computer, a simulation program was assembled on an IBM 370 computer. This model has yielded some interesting results[13], but problems with the solution instability and enormous demands on the machine time could not be overcome. Therefore, further development of this model on a digital computer was stopped.

The use of a hybrid computing system has been found promising for this purpose. Even the first attempts to construct a simulation model of an isotachophoretic separation on an EAI 690 hybrid system were found to be very promising[14]. On the basis of this experience, the simulation model described in this paper was developed and applied during 1976–78.

MATHEMATICAL MODEL

The mathematical description adopted is based on the general equation

$$\frac{\partial c_{j,z}}{\partial t} = D_{j,z}\frac{\partial^2 c_{j,z}}{\partial t^2} + \operatorname{sgn} z \cdot c_{j,z} \cdot \frac{\partial \varphi}{\partial x} \cdot \frac{\partial U_{j,z}}{\partial x} + \\ + \operatorname{sgn} z \cdot U_{j,z} \cdot \frac{\partial \varphi}{\partial x} \cdot \frac{\partial c_{j,z}}{\partial x} - \operatorname{sgn} z \cdot c_{j,z} \cdot U_{j,z} \cdot \frac{\partial^2 \varphi}{\partial x^2} \qquad (1)$$

$$\operatorname{sgn} z = \begin{cases} 1 \text{ for } z > 0 \\ 0 \text{ for } z = 0 \\ -1 \text{ for } z < 0 \end{cases}$$

where the subscripts j,z denote the quantities relating to component j in its ionic form with charge z, c is the concentration, D is the diffusion coefficient, φ is the potential gradient and U is the mobility.

Eqn. 1 has been derived in detail earlier[2,3]; we should only point out that the equation assumes the validity of the electroneutrality condition, does not consider convective and thermal fluxes and neglects the concentration dependence of the diffusion coefficient. A term describing interactions of the components with the carrier is, of course, also not included. As a solution of such a general equation on a computer is very complicated, the following simplifying assumptions have been made.

(a) The separation takes place in a capillary and all the parameters are constant through the capillary cross-section. Hence only two independent variables need be considered in the description of the separation: distance along the capillary (x) and time from the beginning of the separation (t).

(b) The separation proceeds isothermally.

(c) Four electrolytes participate in the separation, the leading and the terminating electrolyte and two components to be separated or representing impurities. All the components have a common counter ion and are strong, uni–univalent electrolytes.

(d) The concentration dependence of the mobilities of the components is negligible.

(e) The concentrations of the H^+ and OH^- ions are negligible compared with those of the ions to be separated.

These assumptions make it possible to simplify eqn. 1 to the form

$$\frac{\partial c_j}{\partial t} = -\frac{J}{F} \cdot U_j \cdot \frac{\partial}{\partial x}\left(\frac{c_j}{S}\right) \qquad \begin{matrix} j = 1, 2, 3, 4 \\ c_j = c_j(x,t) \end{matrix} \tag{2}$$

where J is the current density, F is the Faraday constant and $S = \sum_{i=1}^{4} (U_i + U_R)c_i$, where U_R is the mobility of the counter ion.

Under the above conditions, it is sufficient to simulate the concentrations of four components, *i.e.*, eqn. 2, as the concentration of the counter ion is given by the electroneutrality conditions; hwence no independent partial differential equation need be formulated and solved for the counter ion. If, further, the general Kohlrausch regulating function and the condition of electroneutrality in any point of the column are considered, then it is possible to solve, instead of the fourth partial differential equation in eqn. 2, an algebraic (balance) equation for the fourth component.

COMPUTER SIMULATION TECHNIQUE

An EAI 690 hybrid computing system was used to simulate the ITP separation dynamics. A set of three partial differential equations of the type of eqn. 2, a balance algebraic equation, algebraic equations for the calculation of other parameters and all auxiliary calculations and those connected with the specification of the initial conditions and with graphical output were solved on the computer.

To solve the three partial differential equations (eqn. 2), the classical straight-line method in the continuous space, discrete time arrangement was selected. Each of the partial differential equations was thus replaced with a set of normal differential equations. The distance along the capillary was modelled continuously (by the machine time), whereas the other independent variable, the separation time, was substituted by discrete values t_i ($i = 1, 2, \ldots, n$) at equidistant points, $\Delta t = t_{i+1} - t_i$. Thus the solution of the set of normal differential equations (substituting a single partial differential equation) is not obtained over the whole definition region, $x \in \langle 0,L \rangle$ and $t \in \langle 0,t_{max} \rangle$, but only the straight lines $x \in \langle 0,L \rangle$ for $t = t_i (i = 1, 2, \ldots, n)$. Therefore, for each component the concentration profiles along the capillary are obtained at a time of separation t_i, *i.e.*, $c = c(x, t = t_i)$, $x \in \langle 0,L \rangle$.

On transfer from a partial differential equation to a set of normal differential equations, the partial derivative was replaced by a simple back difference, *i.e.*

$$\frac{\partial c(x,t_i)}{\partial t} \doteq \frac{c(x,t_i) - c(x,t_{i-1})}{\Delta t}$$

Formal rearrangement yielded a set of normal differential equations for each component:

$$\frac{\partial}{\partial x}\left(\frac{c_j^k}{S^k}\right) = -\frac{c_j^k - c_j^{k-1}}{\Delta t} \cdot \frac{F}{U_j \cdot J} \tag{3}$$

where $S^k = \sum_{l=1}^{4} (U_l - U_R)c_l^k$, $c_j^k = c(x, t=t_k)$ for the jth component, $j = 1, 2, 3, 4$ and $k = 1, 2, \ldots, n$.

In the solution of the problem on a hybrid computing system, it is advantageous to solve only a single normal differential equation at a time from the set for each component on the analog part of the system and then to repeat this solution gradually in cooperation with the digital part of the system until the whole set of equations is solved. A block diagram of this procedure is given in Fig. 1.

The main analog program solves the system of three differential equations (one of each of the sets of normal differential equations for three components) and one balance, algebraic equation for the fourth component. Thus the result of the solution in the kth step, *i.e.*, for this separation time, $t = t_k$ is $c_j^k(x)_x$, $j = 1, 2, 3, 4$. In this calculation, the required profiles c_j^{k-1} (*i.e.*, the results of the previous computing step) are fed from the memory of the digital part through digital-to-analog converters and simultaneously the values being computed are stored in the digital memory through

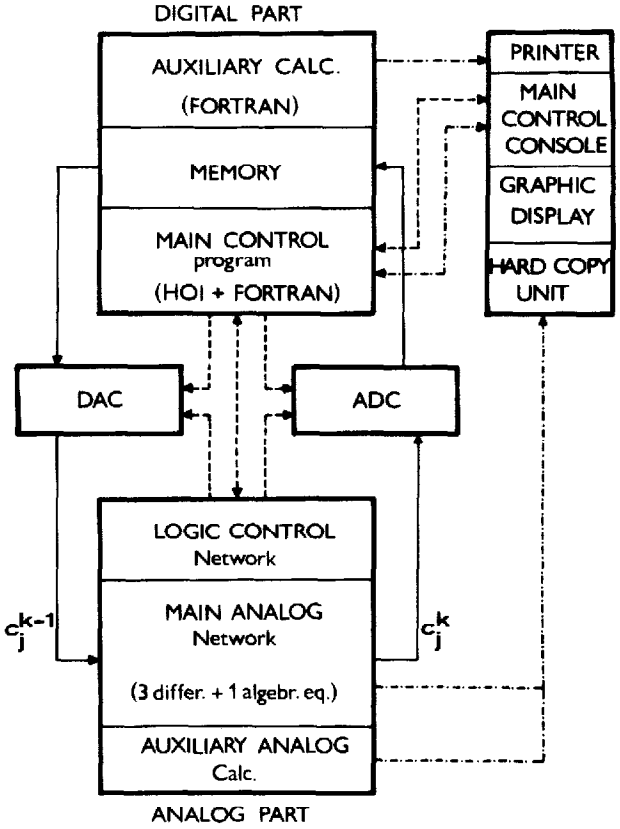

Fig. 1. Block diagram of the isotachophoretic simulation on the EAI 690 hybrid system. ——→, Data transfer; —·—·→, output data; ←·—·→, input/output data; — — →, control signals (one-way); ←— — →, control signals (both ways). c_j^k, concentration of the jth component along the capillary at separation time t_k ($k = 1,2,..,n$). DAC, digital-to-analog converters; ADC, analog-to-digital converters; HOI, hybrid operation interpreter.

analog-to-digital converters, to be used in the next, *i.e.*, the $k+1$th, step. The solution must be repeated as many times as the number of discrete steps t_k used for the replacement of the continuous variable, the separation time (here 300–400 times).

The whole simulation model on the hybrid system consisted of five program parts:

(1) The main operating program (partly in HOI language and partly in FORTRAN, utilizing universal control subroutines SYMHYB), capable of controlling the whole computation, parameter changes and changes of input data and of the graphical output.

(2) A FORTRAN program for auxiliary digital calculations (generation of the initial profiles of the concentrations, transformation of the stored data, etc.).

(3) The main analog program for the solution of three differential and one algebraic equations.

(4) Logic network for the control of the analog calculation, of interpolations, converters and of communications with the digital part.

(5) An auxiliary analog program for interpolations and calculation of further quantities and parameters.

The solution time for each step t_k was *ca.* 1.5 sec. Each of the four stored functions was sampled in 1500 points (*i.e.*, the sampling rate, 1 msec). In the reconstruction of the analog function, linear interpolation was used between the samples. The whole separation time was usually divided into 300–400 steps (t_1–t_{400}), *spaced equidistantly*, $\Delta t = 2$ sec of the separation.

RESULTS

As can be seen from the simulation method, primarily the concentration profiles of all the components along the capillary could be monitored each 2 sec of the separation. For all the concentration profiles, the first four statistical moments were also calculated, by means of which the symmetry of the profiles, movement of the gravity point of the zones, etc., can be followed.

In addition to the concentration profiles, the conductance profiles along the capillary were also calculated for each separation time t_k, from which the theoretical response of the conductivity detector can be reconstructed at a fixed point of the capillary and as a function of time.

For most calculations, the following mobilities of the components were selected:

$U_L = 7.618 \cdot 10^{-4}$ $cm^2sec^{-1}V^{-1}$ (corresponding to the K^+ ion);
$U_A = 5.192 \cdot 10^{-4}$ $cm^2sec^{-1}V^{-1}$ (corresponding to the Na^+ ion);
$U_B = 3.420 \cdot 10^{-4}$ $cm^2sec^{-1}V^{-1}$ [corresponding to the $(C_2H_5)_4N^+$ ion];
$U_T = 1.980 \cdot 10^{-4}$ $cm^2sec^{-1}V^{-1}$ [corresponding to the $(C_4H_9)_4N^+$ ion];
$U_R = 7.913 \cdot 10^{-4}$ $cm^2sec^{-1}V^{-1}$ (corresponding to the Cl^- ion).

The methods for the solution of the mathematical model of the isotachophoretic separation on an analog and a digital computer, described in the Introduction, permitted a study of the dynamics of the boundary between two components. Only the use of a hybrid computing system made it possible to study the dynamics of the isotachophoretic separation of two components placed between the leading and the terminating electrolyte.

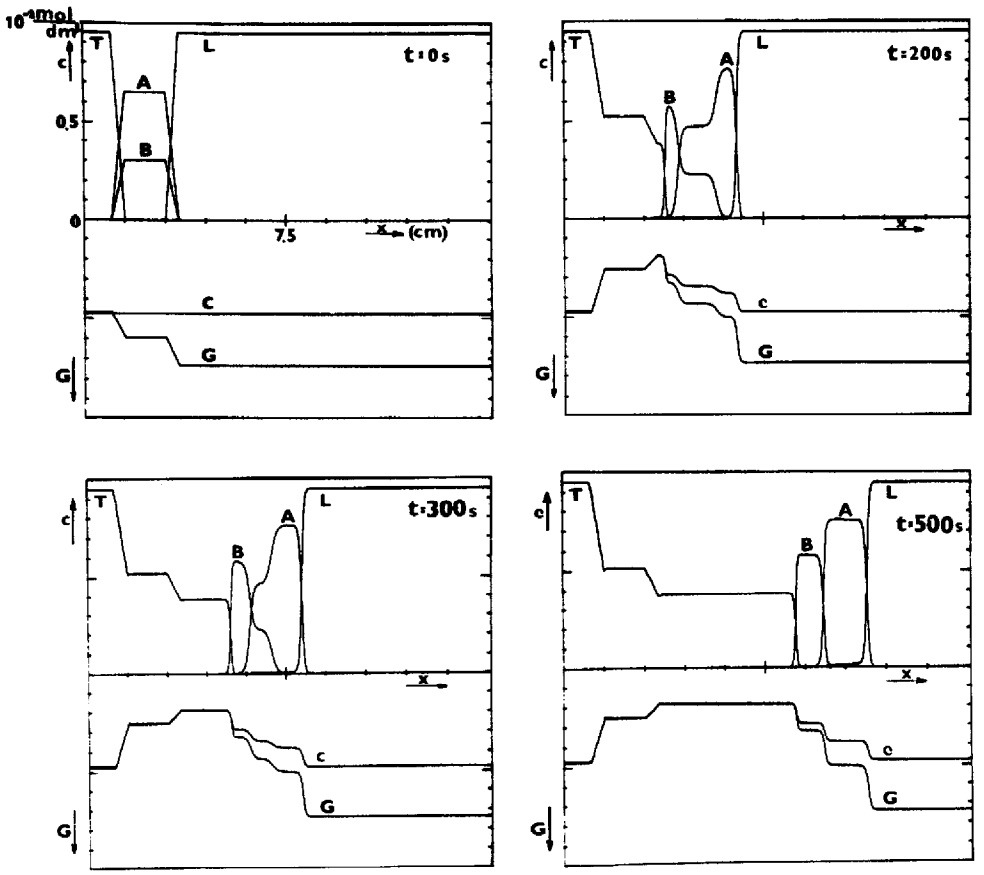

Fig. 2. Example of the simulation calculation. In the upper parts, the concentration profiles of the components are given along the capillary; the bottom parts contain the conductance profiles and the overall concentrations of all the components along the capillary. These recordings can be obtained for a separation time t with a step of 2 sec.

An extension of this mathematical model to include a greater number of separated components would lead to an increase in the complexity of the analog and digital programs and to increased demands on the rate of data storage in the memory of the digital computer.

Using these components, a great variety of separation conditions were modelled. The initial conditions were simultaneously selected, *i.e.*, the concentration profiles at the beginning of the separation. In this way it was possible to simultate not only the isotachophoretic separation under various initial conditions, but also cases when the principle of isotachophoresis is combined with that of displacement electrophoresis (impurities in the leading or terminating electrolyte), etc.

Some results of the simulation of the isotachophoresis dynamics using this model are discussed in ref. 4 and in the following paper[15]. Fig. 2 illustrates a typical result of the simulation of the classical isotachophoretic separation of a mixture of two substances (components A and B) between a leading electrolyte L and a terminating electrolyte T.

DISCUSSION

The results of the simulation of the separation dynamics from the point of view of the theory and applications of isotachophoresis are discussed elsewhere[4,15]. Here only the modelling aspects are considered.

As discussed above, the CSDT (Continuous Space Discrete Time) method with simple back differences was selected for the solution of the partial differential equations because it is most suitable for this purpose. The main advantage of the method is the easy realization of the model on a computer, from the point of view of the programming. On the other hand, the method has one drawbacks, mainly the danger of a substantial accumulation of errors during the calculations (here usually 300–400 calculations for a single simulation run). From this point of view, those parts of the model which control the interpolations during transfers of the functions between the analog and the digital parts and their transformation are critical (points 2 and 5 under Computer Simulation Technique). The error accumulation has been reduced to a negligibble level by suitable procedures, although up to 600 gradual calculations were used in a single simulation run. This can be evaluated readily from the results of the simulation of a classical isotachophoretic separation, as after the attainment of the steady state all the concentration profiles must move without change at a constant rate along the capillary. The simulation model realized fully satisfies this requirement; *e.g.*, the ratio of the concentrations in the zones of the components of the mixture in the steady state is established with an error of 1–2% compared with the theoretical value and is maintained with the same error during the migration along the whole capillary (15 cm).

The set of partial differential equations solved is non-linear. However, the simulation model realized never exhibited traces of instability or distorted the concentration boundaries. Hence the calculation methods used are adequate for the solution of the given problem.

CONCLUSIONS

A computer simulation model was realized on an EAI 690 hybrid computing system for modelling separation dynamics. The precision of the model is satisfactory for all the cases studied. The model is readily variable and can be used, under the given assumptions, for modelling all variants of electrophoretic separations.

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