ANALYSIS BY MIGRATION IN THE PRESENCE OF CHEMICAL REACTION

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INTRODUCTION

In many quantitative analytical techniques (such as electrophoresis, ultracentrifugation, countercurrent distribution, column or paper chromatography, various distillation techniques etc.) a mixture of several species of molecules is analyzed by subjecting it to conditions under which the several species migrate at different rates. In situations where chemical reactions may occur among the several species and where the extents of the reactions are non-negligible these techniques fail in the sense that the usual methods for numerically determining

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the quantities of the various species are not applicable. In such situations the analytical system is ordinarily modified so that no non-negligible reactions occur. However, in some cases a modification of this kind may be either impossible or inconvenient. This paper will present a mathematical framework which under certain circumstances will allow a quantitative analysis, even in the presense of non-negligible chemical reactions amongst the species. This framework will be applicable under the following circumstances:

1) The non-negligible chemical reactions which can occur are known.

2) The reactions which can occur to a non-negligible sense are all sufficiently rapid relative to the rates at which the migratory processes occur, that they may be considered to be instantaneous equilibrium reactions. For this purpose, a one way reaction which is so rapid that it always instantaneously exhausts the supply of at least one of its reactants, may be considered a special case of an equilibrium reaction.

3) A moderately powerful digital computer is available.

The methods described here may well be applicable to systems other than those of analytical chemistry. For example, they may well apply to the analysis of certain systems, in vivo. However, they were developed with chemical analysis in mind.

The material presented here has been given elsewhere, in a more general form, and with a more mathematical orientation [1] .

<u>The Mathematical Framework</u>

Consider N species, $A_1,\ldots,A_i,\ldots,A_N$, of molecules, in solution (either gaseous or liquid) and subject to any number of migratory effects and to chemical reaction. The following assumptions will be made:

<u>Assumption 1</u>: The processes take place in a long "tube" such that the concentration of each A_i is constant in every cross section of the tube perpendicular to the tubes longitudinal axis. That is, the concentration of A_i is a function, $c_i(x,t)$, of only the longitudinal coordinate, x, along the tube, and time, t, where $-\infty < x < \infty$ and $o \leq t < \infty$.

The cross sectional area of the tube will be allowed to depend on both x and t. Let $Q(x,t)$ be the area of the cross section of the tube at x, at time, t.

Assumption 1, embodies a description of the geometry in which the processes are to occur. Actually the methods presented here, are applicable to a much wider class of situations than is indicated by assumption 1 (with rather trivial modifications in the development). For example, instead of a single dimension, x, in which the processes take place, I could, as easily, have chosen several (as would be necessary for certain kinds of paper chromatography) or instead of allowing x to take continous values, I could have restricted x to discrete values, (as would be necessary for counter-current distribution). In [1] a more general geometry is used.

<u>Assumption 2</u>: All the chemical reactions amongst the A_i are either infinitely fast or infinitely slow, relative to the migratory processes. That is, the chemical reactions to which the A_i are subject, fall into two distinct classes:

a) Those whose reaction rates are so large (relative to the migratory rates) that they may be considered to attain equilibrium instantaneously. It will also be assumed that these reactions obey the mass action law. These reactions will be called "fast" reactions.

b) Those whose reaction rates are so small, relative to the migratory rates, that their effects may be neglected.

Assumption 2, unlike assumption 1, is crucial to the developments of this paper. If it is not valid, the methods of this paper will not directly apply.

<u>Assumption 3</u>: The laws under which the various migratory effects take place can be expressed in terms of:

$$x, t, c_1(x,t), \ldots, c_N(x,t), \frac{\partial c_1(x,t)}{\partial x}, \ldots, \frac{\partial c_N(x,t)}{\partial x}.$$

To state assumption 3 more precisely, let $S_i(x,t)$ be the time rate of the number of molecules of A_i which cross x (in the positive direction) at time t, as a result of the totality of migratory effects. (In the literature, the quantity analogous to my S is written as $\frac{\partial S}{\partial t}$, presumably because S is a rate.)

Then, the assumption is, that for appropriate functions s_i:

$$(1) \quad S_i(x,t) = s_i\left(x, t, c_1(x,t), \ldots, c_N(x,t), \frac{\partial c_1(x,t)}{\partial x}, \ldots, \frac{\partial c_N(x,t)}{\partial x}\right)$$

Note that, the dependence of S_i on x and t is due both explicitly to the dependence of s_i on x and t and implicitly to the dependence of s_i on the $c_i(x,t)$.

I believe that this assumption is general enough to embrace almost any situation of interest. (Of course, if assumption 1, is modified, then a corresponding modification of assumption 3 will be necessary. The crucial fact about assumption 3 is that it does not allow $S_i(x,t)$ to depend on time derivatives of the c_i's). For example, if the migration is due to a combination of diffusion and translation it allows the coefficients of diffusion mobility for any of the c_i to depend on all of the other c_i's and their spatial derivatives. It allows the force field causing the translation to vary with position and time.

Consider a reaction to which the A_i are subject. Associate with this reaction an N dimensional vector, $r = (r_i, \ldots, r_N)$ such that the reaction may be written:

$$(2) \quad \sum_{\substack{i \\ r_i > 0}} r_i A_i \rightleftarrows \sum_{\substack{i \\ r_i < 0}} (-r_i) \quad A_i$$

(those unfamiliar with vector analysis should regard a vector as, simply an ordered sequence of numbers). That is, if A_i does not occur in the reaction, let $r_i = 0$, if A_i appears on the left side of the reaction equation, let r_i be the coefficient of A_i, if A_i appears on the right hand side of the reaction equation, then let r_i be the negative of the coefficient of A_i. Note, that given the vector associated with a reaction we can immediately form the equation governing that reaction. Note also, that if a vector r is associated with a reaction, then the vector -r is associated with the reaction obtained by reversing the left and right hand sides of (2).

I will call a vector, r; a <u>reaction vector</u> if it is associated with a "fast" reaction.

Note that, for any reaction vector, r, we have the mass balance equation:

$$(3) \quad \prod_{i=1}^{n} c_i(x,t)^{r_i} = k_r$$

Where k_r is the mass balance constant of the reaction with which r is associated.

Let R be the set of all reaction vectors.

Theorem 1: R is a linear subspace of the set of all n dimensional vectors (that is if r and r^* are members of R, then so is $r + r^*$; and if r is a member of R then so is br, for any scalar b).

Proof: Let r be associated with the fast reaction ρ and r^* with the fast reaction ρ^*. Then, the reaction whose equation is obtained by adding the equations for ρ and ρ^* will be a fast reaction and will be associated with $r + r^*$. Similarly the reaction obtained by multiplying both sides of the reaction equation for ρ by b will be a fast reaction and will be associated with br. Q.E.D.

Theorem 2: Consider a small volume, dV, such that the concentration of each of the A_i may be considered spatially constant within dV. Suppose that concentrations $c_1,\ldots,c_N$ (not necessarily in equilibrium ratios) of the A_i are suddenly placed in dV and that all the fast reactions instantaneously occur producing equilibrium concentrations

$c_1 + \Delta c_1, \ldots, c_N + \Delta c_N$.

Let f be a vector which is perpendicular to every reaction vector, (two vectors are perpendicular if their dot or scalar product is zero).

Then:

$$(4) \quad \sum_i f_i \, \Delta c_i = 0$$

Proof: For any reaction vector, r, let $\Delta_{r,i}$ denote the change in c_i due to the fast reaction associated with r. We have:

(5) $\Delta_{r,i} = e_r \, r_i$, where e_r is a measure of the extent to which the reaction occurred in reaching equilibrium.

Hence:

$$(5) \quad \sum_i f_i \, \Delta_{r,i} = \sum_i f_i \, e_r \, r_i = e_r \sum_i f_i \, r_i = 0$$

Since each Δc_i is the sum over all reaction vectors, r, of the $\Delta_{r,i}$, equation (4) can be obtained by adding equation (5) for all reaction vectors.

Theorem 3: Let f be a vector which is perpendicular to every reaction vector. Then, the following partial differential equation holds:

$$(6) \quad \sum_i f_i \frac{\partial}{\partial t} \Big(c_i(x,t) \quad Q(x,t) \Big) = -\sum_i f_i \frac{\partial S_i(x,t)}{\partial x}$$

Proof: Let dV be the volume between x and x + dx. Note, that the volume of dV is dxQ(x,t). The net number of molecules of A_i which migrate into dV between t and

$t + dt$ is:

$$S_i(x,t)\ dt - S_i(x+dx,t)\ dt = -\frac{\partial S_i(x,t)}{\partial x}\ dx\ dt$$

Imagine that at time t the concentrations within dV are at equilibrium, and that during the interval between t and t + dt migrations are allowed to occur but that no chemical reactions occur until t + dt, when equilibrium is instantaneously reattained. The number of molecules of A_i in dV at time t + dt just before instantaneous reactions occur is then:

$$c_i(x,t)\ Q(x,t)\ dx - \frac{\partial S_i(x,t)}{\partial x}\ dx\ dt$$

and the concentrations c_i are:

$$(7)\quad c_i = \frac{c_i(x,t)\ Q(x,t)\ dx - \frac{\partial S_i(x,t)}{\partial x}\ dx\ dt}{Q(x,t+dt)\ dx}$$

After the reaction takes place, the concentration $c_i + \Delta c_i$ may be expressed in the form:

$$(8)\quad c_i + \Delta c_i = c_i(x,t) + \frac{\partial c_i(x,t)}{\partial t}\ dt$$

subtracting (7) from (8)

$$\Delta c_i = \frac{c_i(x,t)}{Q(x,t+dt)}\Big(Q(x,t+dt) - Q(x,t)\Big) + \frac{\frac{\partial S_i(x,t)}{\partial x}}{Q(x,t+dt)}\ dt + \frac{\partial c_i(x,t)}{\partial t}\ dt$$

or (ignoring higher order terms)

$$(9)\quad \frac{\Delta c_i}{dt}\ Q(x,t) = \frac{\partial}{\partial t}\Big(c_i(x,t)\ Q(x,t)\Big) + \frac{\partial S_i(x,t)}{\partial x}$$

Now apply Theorem 3 to the Δc_i, multiply (6) of

Theorem (3) by $\frac{Q(x,t)}{dt}$ and then use (9) to arrive at (6). Q.E.D.

Returning to the mass balance equation, (3), which holds for every reaction vector, r, note that we can write down an infinite number of equations of this form, since there are an infinite number of possible reaction vectors. (For example, if r is a reaction vector then, by Theorem 1, so is br, for all scalars, b). However, it turns out that all of these equations are not independent. In fact:

<u>Theorem 4</u>: Let r, and r^* be reaction vectors, then the mass balance equation for the reaction associated with $r + r^*$ is obtained by multiplying corresponding sides of the mass balance equations for the reactions associated with r and r^*.

In particular:

$$(10) \quad k_{r + r^*} = k_r \, k_{r^*}$$

Furthermore the mass balance equation for the reaction associated with br is obtainable by taking the b'th power of both sides of the mass balance equation of the reaction associated with r.

In particular:

$$(11) \quad k_{br} = (k_r)^b$$

<u>Proof</u>: Theorem 4 follows from the way in which vectors

are added and multiplied by scalars, and from the form of equation (3).

Let dim R be the dimension of R (the dimension of a linear sub-space is the maximum number of linear independent vectors in the space). Then by Theorem 4, there are exactly dim R independent mass balance equations relating the concentrations $c_i(x,t)$.

Similarly, Theorem 3 seems to indicate that there are an infinite number of partial differential equations of the form, (6), relating the $c_i(x,t)$, since there are an infinite number of vectors perpendicular to every reaction vector. However, any linear relation between f's, will reflect itself as a linear relation amongst the equations of the form (6) induced by those f's. Let $R_{\perp}$ denote the set of all vectors, f, which are perpendicular to every reaction vector. We know from vector analysis that $R_{\perp}$ is also a linear subspace. Let dim $R_{\perp}$ be the dimension of $R_{\perp}$. There are thus only dim $R_{\perp}$ independent partial differential equations of the form, (6). It is a theorem from vector analysis that:

(12) $\quad \dim R + \dim R_{\perp} = N$

We thus have a total of N independent simultaneous relations amongst the $c_i(x,t)$. - dim R independent mass balance equations of the form, (3), and dim $R_\perp$ independent partial differential equations, (6).

The dim R equations (3) can be used to express dim R of the $c_i(x,t)$'s in terms of the remaining (N - dim R = dim $R_\perp$), $c_i(x,t)$'s. Note that, in general there is no guarantee that we can eliminate any particular dim R of the $c_i(x,t)$'s: we only know that we can eliminate some set of (dim R) of the $c_i(x,t)$'s. For example if N = 4, dim R = 2 and the mass balance equations are: (omitting for convenience the arguments x,t)

$$c_1^{-1}\, c_2^{-1}\, c_3^2\, c_4 = k$$

$$c_1^{-1}\, c_2^{-1}\, c_3\, c_4^2 = k^*$$

Then the mass balance equations can not be used to eliminate c_1 and c_2 (that is to solve for c_1 and c_2 in terms of c_3 and c_4). Although they can be used to eliminate any other pair of the c's.

It can also be shown that the question of which dim R of the $c_i(x,t)$'s can be eliminated does not depend on which of the dim R independent mass balance equations are chosen.

I can assume (if necessary by rearranging the order of the $c_i(x,t)$'s) that the last dim R of the $c_i(x,t)$ can be eliminated. That is, that $c_{\dim R_\perp + 1}(x,t),\ldots,c_N(x,t)$

can be expressed in terms of $c_1(x,t),\ldots,c_{\dim R_1}(x,t)$. The last dim R of the $c_i(x,t)$ can then be eliminated from the dim R_1 independent simultaneous partial differential equations, of the form (6).

I have thus far shown that the process involved can, in effect, be expressed in terms of dim R_1 independent simultaneous partial differential equations in the quantities $c_1(x,t),\ldots,c_{\dim R_1}(x,t)$. With this system of partial differential equations we could address ourselves to various problems.

For example:

Problem 1: Given the functions $Q(x,t)$ and s_i (see equation (1) in assumption (3) and given the initial concentrations $c_1(x,0),\ldots,c_{\dim R}(x,0)$; to determine the $c_i(x,t)$, that is, to solve the system of partial differential equations with the $c_i(x,0)$ as boundary values.

Problem 2: Given the functions $Q(x,t)$ and s_i and certain information about the $c_i(x,t)$ to determine the $c_i(x,0)$. That is, to solve the system of partial differential equations given more complex boundary values. This is, in fact, the problem which occurs in quantitative analysis.

Problem 3: Given $Q(x,t)$ and certain information about the $c_i(x,t)$'s to determine the functions s_i, that is, to determine the laws under which the migration occurs.

The most straightforward of these problems is problem 1.

All three problems are of practical importance, various numerical techniques are available for all 3 problems. In this exposition, only problem 1 will be considered. The numerical techniques used in problem 1 will be applicable to more complex problems. In our exposition we shall barely indicate one possible numerical attack.

Solution to problem:

Let $P = \dim R_1$

Let $f^{(1)}, \ldots, f^{(j)}, \ldots, f^{(p)}$, be a set of P independent members of R_1. Then, the system of P partial differential equations takes the form: (see (6))

$$(13) \quad \sum_i f_i^{(j)} \frac{\partial}{\partial t} \left(c_i(x,t) \; Q(x,t) \right) =$$

$$- \sum f_i^{(j)} \frac{\partial S_i(x,t)}{\partial x} \quad \text{for} \quad 1 \leqq j \leqq P$$

If we carry out the differentiation on the left of (13), we obtain:

$$(14) \quad \sum_i f_i^{(j)} \frac{\partial c_i(x,t)}{\partial t} = - \frac{\frac{\partial Q(x,t)}{\partial t}}{Q(x,t)} \sum_i f_i^{(j)} c_i(x,t)$$

$$- \frac{1}{Q(x,t)} \sum_i f_i^{(j)} \frac{\partial S_i(x,t)}{\partial x} \quad \text{for} \quad 1 \leqq j \leqq P$$

We also have, as a result of solving the mass balance equations for the first P of the $c_i(x,t)$'s:

(15) $c_i(x,t) = \theta_i \left(c_1(x,t),\ldots,c_P(x,t)\right)$ for $P + 1 \leqq i \leqq N$

By the partial differentiation of the equations (14) we can express

$\frac{\partial c_i(x,t)}{\partial t}$ for $P + 1 \leqq i \leqq N$ in terms of $c_i(x,t)$ and $\frac{\partial c_i(x,t)}{\partial t}$ for $1 \leqq i \leqq P$.

If this is done, note that the result is linear in the $\frac{\partial c_i(x,t)}{\partial t}$, $1 \leqq i \leqq P$.

If we then use (1) to express the $S_i(x,t)$ in terms of x,t, the $c_i(x,t)$ and $\frac{\partial c_i(x,t)}{\partial x}$ carry out the indicated differentiation of the $S_i(x,t)$ (in practice this indicated differentiation would, perhaps, only be done numerically - but, the exposition is simplified if it is assumed that the indicated differentiation is actually carried out) and eliminate:

$$c_i(x,t), \frac{\partial c_i(x,t)}{\partial x}, \frac{\partial^2 c_i(x,t)}{\partial x^2} \quad \text{for} \quad P + 1 \leqq i \leqq N,$$

the system (14) becomes:

(16) $$\sum_{i=1}^{P} \partial_{j,i}, \frac{\partial c_i(x,t)}{\partial t} = \beta_j \quad \text{for} \quad 1 \leqq j \leqq P$$

where the $\partial_{j,i}$ for $1 \leqq i, j \leqq P$ are known functions of the $c_i(x,t)$,

$$(16) \quad \sum_{i=1}^{P} \partial_{j,i}(C) \frac{\partial c_i(x,t)}{\partial t} = \beta_j(C,C',C'') \quad \text{for} \quad 1 \leqq j \leqq P$$

where C denotes $c_1(x,t),\ldots,c_P(x,t)$,

C' denotes $\dfrac{\partial c_1(x,t)}{\partial x},\ldots,\dfrac{\partial c_P(x,t)}{\partial x}$ and

C'' denotes $\dfrac{\partial^2 c_1(x,t)}{\partial x^2},\ldots,\dfrac{\partial^2 c_P(x,t)}{\partial x^2}$;

and where the $\partial_{j,i}$ and β_j are known functions.

The basic computational procedure to be used in the numerical solution of (16) involves extending the knowledge of the $c_i(x,t_0)$ for a fixed t_0, to a knowledge of the $c_i(x,t_0+\Delta t)$, $c_i(x,2\Delta t)$, $c_i(x,3\Delta t)$....etc. Δt chosen small enough so that the $c_i(x,t)$ for t a multiple of Δt will adequately describe the $c_i(x,t)$.

Thus, assume that the $c_i(x,t_0)$ are known for all x and for a fixed t_0. The C, C' and C'' can be computed by numerical differentiation with respect to x, and $\partial_{j,i}(C)$ and $\beta_j(C,C',C'')$ can be numerically evaluated, thus, numerically determining all the elements in the system, (16), except the $\dfrac{\partial c_i(x,t)}{\partial t}$ But (16) is now a system of linear algebraic equations in the unknown $\dfrac{\partial c_i(x,t_0)}{\partial t}$ which can be numerically solved by standard methods.

We then have:

$$c_i(x,t_0 + \Delta t) = c_i(x,t_0) + \Delta t \ \frac{\partial c_i(x,t_0)}{\partial t}$$

The above computational process, even in the simplest situations, is such that it could only be undertaken by means of a high speed digital computer.

The process that has been described is also somewhat simpler than one which will actually be employed. The exposition has been designed only to indicate the basic ideas involved.

REFERENCES

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