A method of solution for a non-linear diffusion model and for computing the parameters in the model

J. SPOELSTRA and D.J. VAN WYK
Potchefstroom University for CHE, Potchefstroom, South Africa

Abstract: The diffusion of a drug through a skin-like membrane which tends to partially absorb the drug, was modelled by means of a system of strongly coupled nonlinear parabolic differential equations. We present a method of computing the parameters in the model characterizing a particular drug and membrane by an optimization procedure. This method consists of minimizing a quantity measuring the correspondence between the predictions of the model and experimental data, as a function of the parameters. In the method the solution of the differential equations for different sets of parameters is used repeatedly. The equations are solved by an implicit finite difference method employing an iterative procedure at every time step.

1. Introduction

In diffusion experiments made in the pharmaceutical sciences, various researchers have found behaviour that could not be explained by the existing mathematical models [3,1,4]. One such experiment, which clearly exhibits this anomalous behaviour, is one where non-stationary diffusion of a drug from a donor cell, through a membrane, to a receiver cell is considered. This type of experiment was used by various authors [7,5]. As it has also been applied to obtain the data used in this paper, we briefly describe the experiment.

A high concentration of a drug in a saline solution is put in a small cell, the donor cell, divided by a thin membrane from another cell of similar volume, the receiver cell. Initially the membrane is free of the drug, and the receiver cell contains only a saline solution. Both cells are stirred continually. As the drug starts diffusing from the donor cell, the concentration in the membrane rises, and, after a small delay, so does the concentration in the receiver cell. The concentrations in both cells are measured regularly, so that a set of values for the concentration in the donor cell is obtained, decreasing with increasing time, as well as a set of values for the concentration in the receiver cell. The concentration in the receiver cell initially increases as time increases, but after a while it starts decreasing due to the absorption of the drug in the membrane.

It has been mentioned above that the existing mathematical models for diffusion, based on Fick's laws, do not apply to certain cases. These cases include membranes of hairless mouse skin,

human skin and several synthetic membranes, with the diffusing drug one of the higher alcohols, for example 1-octanol. For these cases it has been found [8] that the drug is absorbed in the membrane by a process that is modelled very well on the assumption that the rate of absorption at any point in the membrane is proportional to the concentration of the drug at the point. If the x-axis of a coordinate system is taken in the direction of the normal on the membrane, and if it is assumed that no diffusion takes place through the edges of the membrane, the concentration in the membrane can be considered as a function of time and of the x-coordinate, ignoring the y- and z-coordinates. It is further assumed that the rate of transfer of diffusant in the membrane, per unit area, is proportional to the gradient of the concentration across the membrane. In the cases mentioned above it has been found that the coefficient of proportionality is not constant. It is not only a function of concentration, a case which occurs relatively often, but it is also a rapidly decreasing function of the amount of drug absorbed in the membrane.

2. A mathematical model

Let $c(x, t)$ be the concentration of the drug at a distance x from one face of the membrane at an instant of time t, with $z(x, t)$ denoting the concentration of absorbed drug. As the cells are both being well stirred, their concentrations are functions of time only, say $c_1(t)$ and $c_2(t)$ for the donor and receiver cells respectively. If the membrane has a thickness a, both cells a volume of V, and if g is the coefficient that determines the rate of absorption of drug in the membrane, the assumptions made above lead to the following equations,

$$c_t = [P(z, c)c_x]_x - z_t, \quad 0 < x < a, \quad t > 0,$$

$$z_t = gc, \quad\quad\quad\quad\quad 0 < x < a, \quad t > 0,$$

where $P(z, c)$ is the function determining the coefficient of diffusion, and which could be best described in the following form, with P_0 and b constants [8, pp. 152–192]:

$$P(z, c) = P_0 \, e^{-b[z/\{1+c\}]^2}.$$

For computational purposes a simple transformation to a non-dimensional form applied to the two equations above yields the following system, in which the same symbols have been retained for the transformed variables, with $q = a^2 g / P_0$:

$$c_t = [P(z, c)/P_0 c_x]_x - z_t, \quad 0 < x < 1, \quad t > 0, \tag{1}$$

$$z_t = qc, \quad\quad\quad\quad\quad\quad\quad 0 < x < 1, \quad t > 0. \tag{2}$$

The boundary conditions as discussed by various authors (for example [2, pp. 3–4 and p. 57]) have been found to be applicable in the present circumstances. We denote the area of the membrane in contact with the cells by A and the coefficient of partition by k. The following boundary conditions are obtained, where the transformation mentioned above have been applied (here, $D = Aa/V$):

$$c(0^+, t) = kc_1(t), \quad t > 0, \tag{3}$$

$$c(1^-, t) = kc_2(t), \quad t > 0, \tag{4}$$

$$dc_1/dt = (D/P_0)Pc_x(0^+, t), \quad t > 0, \tag{5}$$

$$dc_2/dt = -(D/P_0)Pc_x(1^-, t), \quad t > 0. \tag{6}$$

With the above-mentioned experimental procedure, the following initial conditions apply, C_0 denoting the initial drug concentration in the donor cell:

$$c_1(0) = C_0, \tag{7}$$

$$c_2(0) = 0, \tag{8}$$

$$c(x, 0^+) = 0, \quad 0 < x < 1. \tag{9}$$

Existence theorems for a system of strongly coupled differential equations which includes (1) and (2), for a few types of boundary conditions, were derived by [6], but in the absence of such theorems for the present type of boundary condition, the system (1)–(9) was solved numerically.

In this system there are a number of unknown parameters for a given membrane and drug, namely the initial value of the diffusion coefficient, P_0, the coefficient of partition, k, the constant determining the rate of absorption, q, the constant b in the function P, as well as the initial concentration C_0, which, for various experimental reasons can only with extreme difficulty be accurately determined beforehand. In the next section we will discuss the numerical method that was found to be the most efficient, an iterative implicit method. A method for determining these parameters for a particular drug and membrane will be considered in Section 4 and, finally, in Section 5, we will discuss the results.

3. A numerical method for solving the equations

We place a rectangular grid over the region $\{(x, t): 0 < x < 1, t > 0\}$ with grid spacings f and h respectively. We denote values of the grid functions, corresponding to values of dependent variables in the grid points, by subscripted uppercase symbols with subscripts (n, m) where $n = -1, 0, 1, \ldots, N + 1$ and where $m = 0, 1, 2, \ldots$, with the values $n = -1$ and $n = N + 1$ corresponding to points outside the region, distant f from the boundaries of the region. We discretise the differential equations by using points halfway between points on the grid. If we set $H = \frac{1}{2}$, we can denote these points by the subscripts $(n + H, m + H)$, $(n + H, m - H)$, etc. In discretizing the differential equation, the values in such 'halfway' points are taken as the averages of the values in nearby points.

In the discretization process the values of the variables at two time levels will be needed, and due to the presence of these values in the non-linear function P, it is necessary to use approximations to the correct values at the next time level, where they occur in P. We use the notation $B_{n,m+1}$ for such an approximation to $C_{n,m+1}$ and $Y_{n,m+1}$ for such an approximation to $Z_{n,m+1}$. These approximations are iteratively refined in the method as will be shown. We define the operator d_x by

$$d_x\{U_{n+H,m}\} = \{U_{n+1,m} - U_{n,m}\}/f,$$

and set

$$P_{n+H,m+H} = P(\{Z_{n+1,m+H} + Z_{n,m+H}\}/2, \{C_{n+1,m+H} + C_{n,m+H}\}/2)/P_0$$

where, in the light of the above remarks, values of the dependent variables in a point, j, $m + H$, halfway between j, m and j, $m + 1$, is taken to be the average of the value of the function at j,

m and of the approximation to the function at j, $m + 1$. We now have the following as the discrete analogue to the equation (1):

$$\frac{C_{n,m+1} - C_{n,m}}{h} = \frac{P_{n+H,m+H}\, d_x\{C_{n+H,m+H}\} - P_{n-H,m+H}\, d_x\{C_{n-H,m+H}\}}{P_0 f} - qC_{n,m+H}.$$

By using averages for the $(m + H)$-values, we obtain:

$$-P_{n-H,m+H}C_{n-1,m+1} + \left[\frac{2f^2}{h} + P_{n-H,m+H} + P_{n+H,m+H} + qf^2\right]C_{n,m+1}$$

$$-P_{n+H,m+H}C_{n+1,m+1}$$

$$= P_{n-H,m+H}C_{n-1,m} + \left[\frac{2f^2}{h} - P_{n-H,m+H} - P_{n+H,m+H} - qf^2\right]C_{n,m}$$

$$+ P_{n+H,m+H}C_{n+1,m}. \tag{10}$$

Equation (2) can be discretized to yield the two relations:

$$Z_{n,m+H} = Z_{n,m} + \{qh/8\}[3C_{n,m} + C_{n,m+1}], \tag{11}$$

$$Z_{n,m+1} = Z_{n,m+H} + \{qh/8\}[C_{n,m} + 3C_{n,m+1}] \quad \text{for } n = 0, 1, 2, \dots, N. \tag{12}$$

The initial values (7), (8) and (9) give the following results, using (4):

$$C_{0,0} = kC_0, \tag{13}$$

$$C_{n,0} = 0, \quad n = 0, 1, 2, \dots, N, \tag{14}$$

$$Z_{n,0} = 0, \quad n = -1, 0, 1, \dots, N + 1. \tag{15}$$

Standard arguments applied to the boundary value (5) yield,

$$\left[\frac{2f^2}{h} + P_{-H,m+H} + P_{H,m+H} + qf^2 + \frac{8f}{khD}\frac{P_{-H,m+H}}{P_{H,m+H} + P_{-H,m+H}}\right]C_{0,m+1}$$

$$-[P_{-H,m+H} + P_{H,m+H}]C_{1,m+1}$$

$$= \left[\frac{2f^2}{h} - P_{-H,m+H} - P_{H,m+H} - qf^2 + \frac{8f}{khD}\frac{P_{-H,m+H}}{P_{H,m+H} + P_{-H,m+H}}\right]C_{0,m}$$

$$-[P_{-H,m+H} + P_{H,m+H}]C_{1,m} \tag{16}$$

and a similar relation is obtained from (6).

As a first approximation to the concentration at any new time level, $(B_{n,m})$, we use the values for $C_{n,m}$ obtained at the previous time level. First approximations for the values of $Z_{n,m}$ (i.e. $Y_{n,m}$), may be obtained by using these approximations in the relations (11).

The tridiagonal system of linear equations consisting of (16), (10) and the relation similar to (16), contains the (known) values at one time level, the approximations B and Y to the values at the next time level, and the (unknown) values at the following time level, and can therefore be solved for the values of C and Z at the $m + 1$ time level. If the approximations B and Y to these values are sufficiently close to the values now obtained, these values are accepted as the solution at the new time level. Otherwise, these values are substituted for the B and Y values, and the process repeated. In practice, convergence occurred in two or three iteration steps, except at the first one or two time levels, where, due to the discontinuity in the initial values, more than ten steps were sometimes required.

4. Computing the parameters in the model

For any choice of the parameters, the values of the concentrations in the donor and in the receiver cell, as predicted by the model, can be obtained for the instants at which the experimental data are known, and the differences between the predicted values and the data at corresponding instants can be determined. These differences may be due to experimental errors, an erroneous model or a bad choice of the parameters. We henceforth call the sum of the squares of these differences *the sum of the squares of the errors* (between model and experiment), denoted by SSQ.

The parameters for a given experiment are computed as that choice of parameters which minimizes the sum of the squares of the errors. The Levenberg–Marquard method, as implemented in the IMSL subroutine ZXSSQ, was found to be effective in minimizing this sum of squares as a function of the five parameters P_0, k, q, b and C_0.

Table 1 shows a typical result of these computations for three experiments. The unit of concentration, c.p.m., is radioactive counts per minute, as the experiments were made with a radioactively marked drug. The same membrane and drug were used in all three the experiments, with the initial concentration differing markedly.

The parameters do not show a great variation, except for b (and of course the initial concentration C_0), and no great dependence on concentration. Nevertheless, to simply take the average of the values of each parameter in the set, would not give reliable results. The reason for this lies in the fact that the complete set of parameters simultaneously determine the minimum of the sum of squares. If the value for P_0 in experiment B were, for example, to be fixed on 8.031 (the value for experiment A) the minimum might then be achieved for k much higher than the value computed in the above table, without necessarily increasing the SSQ significantly.

To compute an average set of parameters that apply to the drug and membrane under consideration and not to a specific experiment alone, a technique of successive minimization was used.

In this technique, the parameter showing the least percentage variation over the various experiments is selected from among the four parameters P_0, k, q and b. Denote this parameter by x_1. In the example above, this would be the parameter k. The average value for x_1 is computed, and henceforth considered as valid for each experiment. Referring to the example, we get the average $k = 81.95$. With x_1 fixed, the sum of the squares of the errors is minimized as a

Table 1
Parameters minimizing the sum of squares of the errors

Parameter	Experiment			Units
	A	B	C	
P_0	8.031	7.295	9.227	$cm^2/min \times 10^{-6}$
k	83.25	83.97	78.62	
b	1.220	2.038	1.292	
q	1.255	1.037	1.185	
C_0	210280	102878	197556	c.p.m.
SSQ	160.3	27.9	101.5	$(c.p.m.)^2 \times 10^6$

Table 2
Computing average values of the parameters

	Experiment			Units
	A	B	C	
$(k = 81.95)$				
P_0	8.139	7.444	8.878	$cm^2/min \times 10^{-6}$
b	1.168	1.885	1.447	
q	1.268	1.061	1.150	
C_0	209769	102494	198713	c.p.m.
SSQ	160.5	28.0	102.4	$(c.p.m.)^2 \times 10^6$
$(k = 81.95, q = 1.160)$				
P_0	8.175	7.438	8.876	$cm^2/min \times 10^{-6}$
b	1.317	1.666	1.431	
C_0	209163	102800	198773	c.p.m.
SSQ	166.0	29.1	102.5	$(c.p.m.)^2 \times 10^6$
$(k = 81.95, q = 1.160, P_0 = 8.163 \, cm^2/min \times 10^{-6})$				
b	1.315	1.788	1.368	
C_0	209103	104620	195461	c.p.m.
SSQ	166.0	33.9	117.3	$(c.p.m.)^2 \times 10^6$
$(k = 81.95, q = 1.160, P_0 = 8.163 \, cm^2/min \times 10^{-6}, b = 1.490)$				
C_0	208699	104942	195198	c.p.m.
SSQ	170.0	36.2	119.1	$(c.p.m.)^2 \times 10^6$

function of the remaining parameters. As is shown in Table 2, the changes in the sum of squares for the experiments concerned are almost negligible. Furthermore, the variations in the other parameters have also shown a decrease. The parameter exhibiting the least variation among the remaining 'free' parameters, say x_2, is then chosen. The average of the different values of x_2 is then computed and used as the new fixed value of x_2. In the example, this is q, and its average is 1.160. This process is repeated until only C_0 remains as parameter in the minization process. The whole process applied to the previous example is shown in Table 2.

5. Results

The model was also solved with two other numerical methods, a direct implicit method as well as an iterative Crank–Nicolson method. All these methods were applied with a large number of different grid spacings, and the solutions of all three methods apparently converged to the same limit as the grid spacings decreased. The method discussed in Section 3 was found to be the most efficient, regarding speed and reliability. Numerical experimentation indicated that the best results were obtained with mesh ratio $h/f^2 = 1$, and a grid spacing $f = \frac{1}{80}$ was found to give a
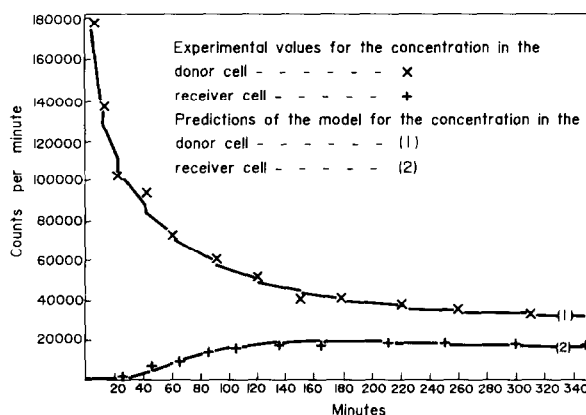
Fig. 1. The correspondence between model and data with average values for the parameters, for experiment A.

more than sufficiently high accuracy. To obtain the same accuracy with the Crank–Nicolson method took approximately twice as long. As the method for computing the parameters called for repeated solutions to the system with different sets of parameters, the method of Section 2 was preferred for solving the system, and the explicit and Crank–Nicolson methods were merely used as controls at different stages of evaluating the model.

The parameters, computed from experiments A, B and C according to the above method, have been substituted in the model and applied to various other experiments. The fit between data and model obtained, was consistently as close as illustrated in Fig. 1. From these results we concluded that the method of determining the parameters described here, was a reliable method to determine the values characterizing the diffusion process for a given drug and membrane.

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