

# Spin-echoes for diffusion in bounded, heterogeneous media: A numerical study<sup>a)</sup>

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The diffusive behavior of spin-bearing species in a bounded heterogeneous medium is analyzed in a manner appropriate for spin echo experiments in the presence of field gradients. A numerical method based upon the stochastic Liouville equation (SLE) is discussed that includes the discontinuities in transport and solubility properties due to the different spatial regions. The double step computational algorithm, which takes advantage of the different time scales of diffusive and spin-quantum phenomena, is then introduced as a general approximate solution of the time dependent SLE. This method is applied to the calculation of the decay of spin echo amplitudes, and it suggests a new approach for analyzing such experiments in terms of the microscopic details and chemical properties of heterogeneous systems.

## I. INTRODUCTION

The NMR spin-echo technique<sup>1-5</sup> offers an accurate measure of the diffusion of nuclear spin-bearing species. This has led to the study of restricted diffusion in a bounded medium<sup>6-9</sup> and in colloidal systems.<sup>10</sup> Spin-echo measurements may be applied to the determination of the physical characteristics of heterogeneous systems of, for example, biological interest,<sup>11,12</sup> while also aiding in the elucidation of biological metabolic processes.<sup>13</sup> In particular, samples containing membranes or sets of membranes seem appropriate for experimental study,<sup>14</sup> but the previous theoretical treatments<sup>5-10</sup> are inadequate for dealing with the complex diffusive properties of such materials and how this affects the spin-echo decays. Analytical mathematical solutions exist only for the simplest of models.

In a recent study which highlighted these difficulties, Tanner<sup>15</sup> discussed the calculation of an apparent diffusion coefficient [i.e., a time-dependent  $D(t)$ ] when one-dimensional diffusion is hindered by equally spaced barriers of arbitrary permeability. Similar strategies were employed by Tanner<sup>15</sup> as in earlier works by others<sup>7,10-12</sup> to obtain apparent diffusion coefficients from theoretical results (or experimental data). By this method, one fits the observed results to an available mathematical relation for the echo amplitude derived using a theory assuming a homogeneous bounded (or infinite) medium. The logarithm of the echo amplitude is usually linear in the diffusion coefficient for these simple cases, so the calculation of an apparent  $D$ , or  $D(t)$ ,<sup>15</sup> attributed to the net effects within the entire sample, is straightforward. However, we shall present an approach which permits more realistic modeling of the heterogeneous nature of the sample.

In this work, we shall discuss the theoretical and numerical construction of models of a heterogeneous bounded medium and the calculation of the resulting spin-echo amplitudes. The spin-echo phenomenon will be studied by focusing on molecules containing a single unpaired nuclear spin (i.e.,  $I=1/2$ , the case of a pro-

ton, is chosen here for simplicity) for which a density matrix formalism<sup>16</sup> will be used to determine the time and spatial dependence of the diffusing spins. The stochastic-Liouville equation (SLE), which describes the diffusive and quantum mechanical time evolution of the spin density matrix elements,<sup>17</sup> will be applied with time dependent solutions calculated via a new approximate numerical method that is applicable for time dependent solutions of the SLE.<sup>18</sup> The models that may be analyzed by this method may contain an arbitrary number of membranes of finite thickness in which the spin-bearing molecule has different diffusive characteristics and solubilities relative to the surrounding medium. The methods outlined here allow the possibility of numerically simulating realistic systems if some, but not all, of their physical characteristics are known, as is commonly the case.<sup>11</sup> These characteristics include membrane widths, sample packing characteristics, diffusion coefficients or solubilities inside or outside the membranes, and any other physical properties included in the model. One would then attempt to match the observed spin-echo decay to a set of numerically determined results for a range of values of the unknown physical characteristics. Since our approach may be applied to models which simulate highly complicated cases, we shall limit our study to the development of the appropriate theoretical tools and conclude with the analysis of several illustrative examples.

## II. THEORETICAL DETAILS

### A. SLE and spin-echo theory

The application of the SLE to the NMR spin-echo problem is directly related to the Bloch equation formalism used in earlier works,<sup>3,8</sup> and for spin 1/2 nuclei leads to identical results. We shall start with a general form of the SLE that contains no reactive sink terms

$$\frac{\partial \hat{\rho}(\mathbf{r}, t')}{\partial t'} = -\mathcal{H}(\mathbf{r}) \hat{\rho}(\mathbf{r}, t') + D \nabla_{\mathbf{r}}^2 \hat{\rho}(\mathbf{r}, t') \quad (1)$$

where we use the superoperator notation  $A^*B \equiv [A, B]$  to denote the commutator of the spin Hamiltonian operator  $\mathcal{H}(\mathbf{r})$ , and the density operator

$$\hat{\rho}(\mathbf{r}, t') = \sum_{i,j} |i\rangle C_i(\mathbf{r}, t') C_j^*(\mathbf{r}, t') \langle j| \quad (2)$$

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where we define the density matrix elements

$$\bar{\rho}_{ij}(\mathbf{r}, t') \equiv C_i(\mathbf{r}, t') C_j^*(\mathbf{r}, t'), \quad (3)$$

with the  $C_i(\mathbf{r}, t')$  being coefficients of the system wave function expanded in terms of the spin functions  $|i\rangle$ . In Eq. (2), we have used bra-ket notation and a bar to denote an ensemble average. For a proton, the spin magnetic moment may be  $M_I = \pm 1/2$ , specified below by  $\alpha (M_I = +1/2)$  and  $\beta (M_I = -1/2)$ , and spin states  $|\alpha\rangle$  or  $|\beta\rangle$ .  $\Gamma_r$  is the diffusion operator with  $D$  a diffusion coefficient. We shall write Eq. (1) for every different region of space for which the spin-bearing molecule has a different  $D$  and/or solubility. These regions will be linked by interfacial regions which have physical properties intermediate between those of the surrounding regions. Examples of this construction are found in Figs. 1 and 3.

If there are  $K$  total regions with the constant diffusion coefficients  $D_k (k=1, 2, \dots, K)$ , then within each respective region the spatial variation in  $D$  that normally enters Eq. (1) via the  $\nabla \cdot \mathbf{D} \cdot \nabla$  operator can be removed. The actual change in the diffusion coefficients across each interface will be included below in a rigorous but practical manner using finite difference arguments. Since a magnetic field gradient in a single direction is usually employed in spin-echo studies, we can reduce the dimensionality of the operator equation [Eq. (1)] and calculate its matrix elements yielding

$$\frac{\partial \bar{\rho}_{kl}(x, t')}{\partial t} = \sum_{i,j} \left[ -\frac{1}{\hbar} \mathcal{K}_{ki,ij}^x(x) + D \Gamma_x \delta_{ki} \cdot \delta_{ij} \right] \bar{\rho}_{ij}(x, t') \quad (4)$$

for all  $k, l = \alpha$  or  $\beta$  with

$$\mathcal{K}_{ki,ij}^x = (\mathcal{K}_{ki}^x \delta_{jl} - \delta_{ki} \mathcal{K}_{jl}^x), \quad (5)$$

and for this problem the Hamiltonian matrix elements  $\mathcal{K}_{ij} \equiv \langle i | \mathcal{H} | j \rangle$  are

$$\begin{array}{c} \langle \alpha | \\ \langle \beta | \end{array} \begin{array}{cc} | \alpha \rangle & | \beta \rangle \\ \left( \begin{array}{cc} -\frac{\hbar}{2} \gamma (H_0 + gx) & 0 \\ 0 & +\frac{\hbar}{2} \gamma (H_0 + gx) \end{array} \right) & \end{array}, \quad (6)$$

with the nuclear magnetogyric ratio  $\gamma = g_N \beta_N / \hbar$ , static magnetic field  $H_0$ , and magnetic field gradient  $g$  in the  $x$  direction which for simplicity in the present discussion we take as perpendicular to the simulated barriers, interfaces, membranes, and walls of the model. Also, the Smoluchowski form of the diffusion operator is<sup>17</sup>

$$\Gamma_x = \frac{\partial^2 \sim}{\partial x^2} - \frac{\partial}{\partial x} [F(x) \sim], \quad (7)$$

where  $F(x)$  is a force on the spin-bearing molecule associated with the different physical properties of the different phases (see below). If we temporarily ignore the heterogeneity of the problem, Eqs. (4)–(7) combine to give

$$\begin{aligned} \frac{\partial \bar{\rho}_{\alpha\alpha}(x, t')}{\partial t} &= D \frac{\partial^2 \bar{\rho}_{\alpha\alpha}(x, t')}{\partial x^2} - D \frac{\partial [F(x) \bar{\rho}_{\alpha\alpha}(x, t')]}{\partial x} \\ &\quad - \frac{[\bar{\rho}_{\alpha\alpha}(x, t') - \bar{\rho}_{\alpha\alpha,0}(x, t')]}{T_1}, \end{aligned} \quad (8a)$$

$$\begin{aligned} \frac{\partial \bar{\rho}_{\beta\beta}(x, t')}{\partial t} &= D \frac{\partial^2 \bar{\rho}_{\beta\beta}(x, t')}{\partial x^2} - D \frac{\partial [F(x) \bar{\rho}_{\beta\beta}(x, t')]}{\partial x} \\ &\quad - \frac{[\bar{\rho}_{\beta\beta}(x, t') - \bar{\rho}_{\beta\beta,0}(x, t')]}{T_1}, \end{aligned} \quad (8c)$$

$$\begin{aligned} \frac{\partial \bar{\rho}_{\beta\alpha}(x, t')}{\partial t} &= -i\gamma(H_0 + gx) \bar{\rho}_{\beta\alpha}(x, t') \\ &\quad + \frac{D \partial^2 \bar{\rho}_{\beta\alpha}(x, t')}{\partial x^2} - D \frac{\partial [F(x) \bar{\rho}_{\beta\alpha}(x, t')]}{\partial x} - \frac{\bar{\rho}_{\beta\alpha}(x, t')}{T_2}, \end{aligned} \quad (8c)$$

and  $\bar{\rho}_{\alpha\beta} = (\bar{\rho}_{\beta\alpha})^*$  due to the Hermiticity of the density matrix. The last terms of Eqs. (8) describe the longitudinal and transverse relaxation of the spins and are added in an *ad hoc* fashion, with  $\bar{\rho}_{\alpha\alpha,0}(x, t')$  representing the equilibrium value of  $\bar{\rho}_{\alpha\alpha}(x, t')$ . After the  $\pi/2$  pulse (chosen to occur at  $t' = 0$ ),  $\rho_{\alpha\alpha}(x, 0) = \bar{\rho}_{\beta\beta}(x, 0) = \frac{1}{2}$  and  $\bar{\rho}_{\beta\alpha}(x, 0) = 1$  since  $M = M_x + iM_y = N_s \text{Tr}[\rho I^+] = N_s \rho_{\beta\alpha}$ , where the "step up" operator  $I^+ = I_x + iI_y$  is used and the  $x$  axis is chosen as the axis of observation with the rf pulses producing rotations about the  $y$  axis.  $N_s$  equals the total number of unpaired nuclear spins in the actual sample. The effect of an instantaneous  $\pi$  pulse can be simulated<sup>8</sup> by  $\bar{\rho}_{\beta\alpha}(x, t'$  after pulse) =  $-\bar{\rho}_{\beta\alpha}^*(x, t'$  before pulse). Furthermore, the echo amplitude at time  $2\tau$ , i.e.,  $F(2\tau)$ , is given by

$$F(2\tau) = \text{Re} \int_{\text{all } x \text{ within sample}} \bar{\rho}_{\beta\alpha}(x, \tau) dx, \quad (9)$$

so we need only consider  $\bar{\rho}_{\beta\alpha}(x, t')$  in any subsequent analysis.

Then, by employing the transformation

$$\rho_{\beta\alpha}(x, t') = \exp[+(i\gamma H_0 + T_2^{-1}) t'] \bar{\rho}_{\beta\alpha}(x, t'), \quad (10)$$

Eq. (8c) becomes

$$\begin{aligned} \frac{\partial \rho_{\beta\alpha}(x, t')}{\partial t} &= -i\gamma g x \rho_{\beta\alpha}(x, t') \\ &\quad + \frac{D \partial^2 \rho_{\beta\alpha}(x, t')}{\partial x^2} - \frac{D \partial [F(x) \rho_{\beta\alpha}(x, t')]}{\partial x}. \end{aligned} \quad (11)$$

By using the simplifying transformation of Eq. (10) in our following discussion and examples, we assume that the relaxation rate  $T_2^{-1}$  is constant throughout each spatially homogeneous region. In the consideration of more complex models, this may be undesirable, but we note that the explicit inclusion of spatially varying relaxation rates in the numerical approach does not create any difficulties. We may now display the theoretical framework in terms of the natural dimensionless variables applicable in this bounded problem.<sup>8</sup> If we measure distance in units of  $a$ , where  $a$  is the width of the entire sample in the  $x$  direction (i.e.,  $0 \leq x \leq 1$ ), then the other intrinsic dimensionless variables are  $t = t' a^2 / D_0$ ,  $\alpha = \gamma g a^3 / D_0$ , and  $f(x) = aF(x)$ , with  $D_0$  being one of the  $D_k$  (e.g., the diffusion coefficient of water  $D_w$ ) chosen arbitrarily and utilized only to properly scale these quantities. Equation (11) can now be written for the  $k$ th region in our model as

$$\begin{aligned} \frac{\partial \rho_{\beta\alpha}(x, t)}{\partial t} &= -i\alpha x \rho_{\beta\alpha}(x, t) \\ &\quad + \frac{D_k^* \partial^2 \rho_{\beta\alpha}(x, t)}{\partial x^2} - \frac{D_k^* \partial [f(x) \rho_{\beta\alpha}(x, t)]}{\partial x}, \end{aligned} \quad (12)$$

where  $D_k^* = D_k / D_0$ .

## B. Finite difference method

We can reformulate the spatial portion of the diffusion operator  $\Gamma_x$  in FD terms using the analogous forms<sup>17,19</sup>

$$\frac{\partial^2 \rho_{\beta\alpha}(x, t)}{\partial x^2} \Big|_{x_l} \rightarrow \frac{\rho_{\beta\alpha}(l+1, t) - 2\rho_{\beta\alpha}(l, t) + \rho_{\beta\alpha}(l-1, t)}{(\Delta x)^2}, \quad (13a)$$

$$\frac{\partial}{\partial x} [f(x)\rho_{\beta\alpha}(x, t)] \Big|_{x_l} \rightarrow \frac{f(l+1)\rho_{\beta\alpha}(l+1) - f(l-1)\rho_{\beta\alpha}(l-1)}{2\Delta x}, \quad (13b)$$

with the FD nodal distance  $x_l = l\Delta x$ .<sup>20</sup> Also,  $\Delta x = x_{l+1} - x_l$ ,  $l$  is the nodal index, and we have used the shorthand notation, for example,  $\rho_{\beta\alpha}(x_l, t) \rightarrow \rho_{\beta\alpha}(l, t)$  to denote the FD nodal value of a quantity. In the FD form, we can rewrite Eq. (12) in terms of the vector  $\rho_{\beta\alpha}$  with elements  $\rho_{\beta\alpha}(l, t)$  for  $l=1$  to  $N$ , with  $N$  being the total number of nodes or FD spatial divisions.

The Hamiltonian superoperator and diffusion operator correspondingly become matrix operators which operate on  $\rho_{\beta\alpha}$ . In order to describe the elements of these matrices when  $x$  space may contain regions with different physical properties, we have chosen an example shown in Fig. 1. This is a case with one interface (now an interfacial node) and two regions, in which the spin-bearing species exhibits diffusion coefficients of  $D_I$  and  $D_{II}$ , respectively. A difference in the solubility of the species in region II relative to region I is simulated by using a potential energy  $U(x)$  in region II (while that for region I is taken as the arbitrary zero). Using a step-function form for  $U(x)$ , i. e.,

$$U(x) = \begin{cases} 0, & x < x_1, \\ U, & x \geq x_1, \end{cases} \quad (14a)$$

the dimensionless force is then

$$f(x) \equiv \frac{-1}{k_B T} \frac{\partial U(x)}{\partial x} = \frac{-\delta(x - x_1)U}{k_B T}, \quad (14b)$$

where  $k_B$  is Boltzmann's constant and  $T$  is the temperature. In FD terms with the Kronecker delta replacing the Dirac delta function, we then have

$$f(l) = (-U/k_B T)\delta_{l,i}, \quad (14c)$$

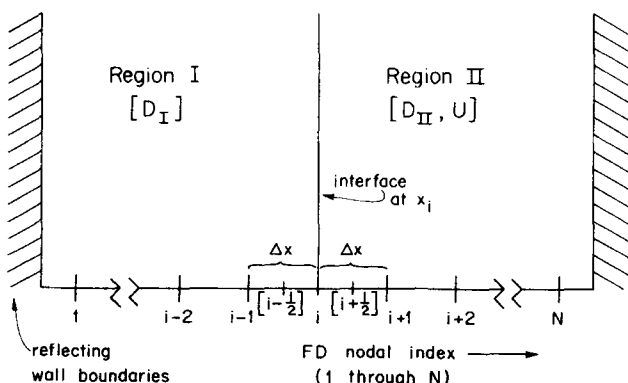


FIG. 1. A bounded, two region model system with a single interface. The FD nodes near the interface are indicated.

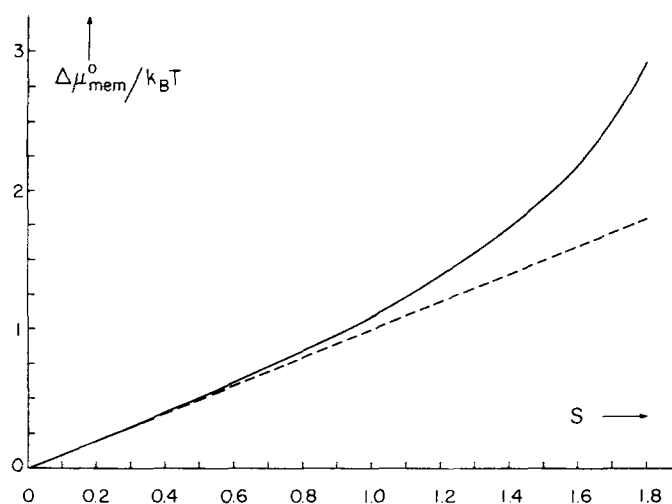


FIG. 2. Chemical potential of a membrane  $\Delta\mu_{\text{mem}}^0/k_B T$  calculated from actual numerical results of systems in equilibrium versus the program input parameter  $S$  (solid curve). The dashed line represents the approximation  $\Delta\mu_{\text{mem}}^0/k_B T \approx S$ .

where the interface is located at the  $i$ th node. This method of simulating a membrane utilizing an energy barrier was proposed by Danielli<sup>21</sup> (who also applied a similar energy barrier approach to model jump diffusion between locations in the sample where diffusing particles encounter an energy minimum). We have found from our calculations that it is useful to define a model parameter  $S \equiv U\Delta x/k_B T$ . The  $\ln(C_{IIq}^{\text{eq}}/C_{\text{mem}}^{\text{eq}})$ , where  $C_{IIq}^{\text{eq}}$  and  $C_{\text{mem}}^{\text{eq}}$  are the equilibrium concentrations of the solute in the outer liquid medium and membrane, respectively, is found to be a simple function of  $S$  (i. e., the logarithm depends upon  $U$  and  $\Delta x$  only via their product). We now introduce the (standard state) membrane chemical potential from equilibrium considerations by

$$\frac{\Delta\mu_{\text{mem}}^0}{k_B T} = \ln K_{\text{eq}}, \quad (15a)$$

where

$$\Delta\mu_{\text{mem}}^0 \equiv \mu_{\text{mem}}^0 - \mu_{IIq}^0 \quad (15b)$$

and the partition coefficient is

$$K_{\text{eq}} \equiv C_{IIq}^{\text{eq}}/C_{\text{mem}}^{\text{eq}}. \quad (15c)$$

We show in Fig. 2 the relationship between  $S$  and  $\Delta\mu_{\text{mem}}^0$  calculated from the equilibrium concentrations. For small enough  $S$ , the two are equal as one might expect, but for  $S > 0.5$  they deviate. This is due to the effect of the interface of finite but small thickness  $\Delta x$  in our FD approach. (It is straightforward from our analysis to model interfaces of finite thickness in more detail than that employed here.)

As we see in Fig. 1, the interface<sup>22</sup> lies between regions with differing diffusional characteristics. Equations (13)–(15) must reflect this feature when transforming from continuous to FD on  $x$ . Utilizing fluxes calculated at  $x_i \pm \Delta x/2$  (referred to as the  $i \pm \frac{1}{2}$  nodes in FD notation<sup>19</sup>), we can use a form similar to Eq. (13a):

$$\left\{ D \frac{\partial}{\partial x} \left[ \frac{\partial \rho_{\beta\alpha}(x, t)}{\partial x} \right] \right\} \Big|_{x_i} - \frac{1}{\Delta x} \left\{ D_{II} \left[ \frac{\partial \rho_{\beta\alpha}(x, t)}{\partial x} \right] \right\} \Big|_{x_i + (\Delta x/2)} - D_I \left[ \frac{\partial \rho_{\beta\alpha}(x, t)}{\partial x} \right] \Big|_{x_i - (\Delta x/2)} \right\} = \left[ \frac{D_I}{(\Delta x)^2} \right] \rho_{\beta\alpha}(i-1, t) - \left[ \frac{D_I + D_{II}}{(\Delta x)^2} \right] \rho_{\beta\alpha}(i, t) + \left[ \frac{D_{II}}{(\Delta x)^2} \right] \rho_{\beta\alpha}(i+1, t), \quad (16)$$

where the central difference form of each derivative is always used. For example,

$$\frac{\partial f(x)}{\partial x} \Big|_{x_i + (\Delta x/2)} \rightarrow \frac{f(i+1) - f(i)}{\Delta x}. \quad (17)$$

Likewise, for the force terms analogous to Eq. (13b), we will use

$$\left\{ \frac{\partial [Df(x)\rho_{\beta\alpha}(x, t)]}{\partial x} \right\} \Big|_{x_i} - \frac{1}{\Delta x} \left[ D_{II} f \left( x_i + \frac{\Delta x}{2} \right) \rho_{\beta\alpha} \left( x_i + \frac{\Delta x}{2}, t \right) - D_I f \left( x_i - \frac{\Delta x}{2} \right) \rho_{\beta\alpha} \left( x_i - \frac{\Delta x}{2}, t \right) \right] = \left[ \frac{(D_{II} - D_I)f(i)}{2\Delta x} \right] \rho_{\beta\alpha}(i, t), \quad (18)$$

noting all terms including  $f(l)$  are zero by virtue of Eq. (15) except when  $l=i$ . Also used in Eq. (18) is the averaging {for example,  $f[x_i + (\Delta x/2)] = [f(i+1) + f(i)]/2$ } needed to describe the derivative of nodal quantities.

The result of Eq. (18) can also be obtained from considerations of the conservation of total probability (or concentration) (provided there are no "sink" terms included in the model).

The FD form of Eq. (12) utilizing matrix operators is

$$\rho = [-i\Omega + \mathbf{W}]\rho, \quad (19)$$

with the nodal index ranging as  $1 \leq l \leq N$ , so the vector  $\rho$  is given by

$$\rho = \begin{pmatrix} \rho_{\beta\alpha}(1, t) \\ \rho_{\beta\alpha}(2, t) \\ \vdots \\ \rho_{\beta\alpha}(N, t) \end{pmatrix}. \quad (20)$$

Similar to past studies<sup>17</sup> employing numerical solutions of the SLE, the quantum mechanical operators will be included in  $\Omega$  with all pure diffusive terms in  $\mathbf{W}$ , the "transition" matrix.<sup>23</sup> For this problem,  $\Delta t W_{i,i\pm 1}$  represents approximately the probability of a particle jumping from the region immediately surrounding the  $(l \pm 1)$ th node into the region near the  $l$ th node over a span of time equal to  $\Delta t$ . The quantity  $1 + \Delta t W_{i,i}$  consequently specifies the probability that the particle originally near the  $l$ th node will be found there after  $\Delta t$  has passed.<sup>24</sup> Conservation of total probability may then be expressed by

$$\sum_k W_{i,k} = 0, \quad \text{for all } l. \quad (21)$$

This may be rewritten in terms of the discussion above, assuming only  $W_{i,i}$  and  $W_{i,i\pm 1}$  are nonzero as

$$(1 + \Delta t W_{i,i}) + \Delta t (W_{i-1,i} + W_{i+1,i}) = 1, \quad (22)$$

or there is unit probability of a particle near the  $l$ th node being present at some location after  $\Delta t$ . Equation (19) represents a supermatrix<sup>17</sup> construction applicable to arbitrary sized basis sets (i.e., any number of density matrix elements) with straightforward modifications. From Eq. (12), the elements of  $\Omega$  are given by

$$\Omega_{i,j} = \alpha x_i \delta_{i,j} \quad (23)$$

and are unaffected by the variation in regional diffusive properties. These latter effects are found in  $\mathbf{W}$ , which for the case shown in Fig. 1 is, by virtue of Eqs. (13)–(18),

$$W_{i,i} = -2/(\Delta x)^2, \quad (24a)$$

$$W_{i,i\pm 1} = 1/(\Delta x)^2 \quad (24b)$$

for  $l < i$  except for

$$W_{i,i} = -1/(\Delta x)^2, \quad (24c)$$

$$W_{i-1,i} = 1/(\Delta x)^2 - f(i)/2\Delta x. \quad (24d)$$

The elements for the interfacial node are

$$W_{i,i-1} = 1/(\Delta x)^2, \quad (24e)$$

$$W_{i,i} = -(1 + D_{II}^*)/(\Delta x)^2 + (1 - D_{II}^*)f(i)/2\Delta x, \quad (24f)$$

$$W_{i,i+1} = D_{II}^*/(\Delta x)^2, \quad (24g)$$

where  $D_{II}^* = D_{II}/D_I$ . The elements specifying region II are

$$W_{i,i} = -2D_{II}^*/(\Delta x)^2, \quad (24h)$$

$$W_{i,i\pm 1} = D_{II}^*/(\Delta x)^2 \quad (24i)$$

for  $l > i$  except for

$$W_{i+1,i} = D_{II}^*/(\Delta x)^2 + f(i)/2\Delta x, \quad (24j)$$

$$W_{N,N} = -D_{II}^*/(\Delta x)^2. \quad (24k)$$

In order to emphasize the broad range of biophysical problems for which this numerical method of analysis is applicable, we can also insert terms which simulate "facilitated" diffusion pathways.<sup>25</sup> Such phenomena can be included via adding the matrix  $\mathbf{K}$  to the operators of Eq. (19). For example, if particles were transported from around node  $j$  to node  $l$  by some process that could be described by the first order rate law

$$- \frac{d\rho_{\beta\alpha}(j, t)}{dt} = \frac{d\rho_{\beta\alpha}(l, t)}{dt} = k\rho_{\beta\alpha}(j, t), \quad (25)$$

then  $\mathbf{K}$  would contain all zero-valued matrix elements except for the elements

$$K_{j,j} = -K_{l,l} = -k. \quad (26)$$

The construction of the  $\mathbf{W}$  matrix for the two membrane (or five region) system under study in Sec. III [see Fig. 3(a)] follows the logic displayed in simulating the system shown in Fig. 1, except that in this more complex case four interfaces are necessary and one must account for the varying diffusion coefficients in the manner used to obtain Eqs. (24). Also, it is important to note that, instead of Eq. (14c), we now have

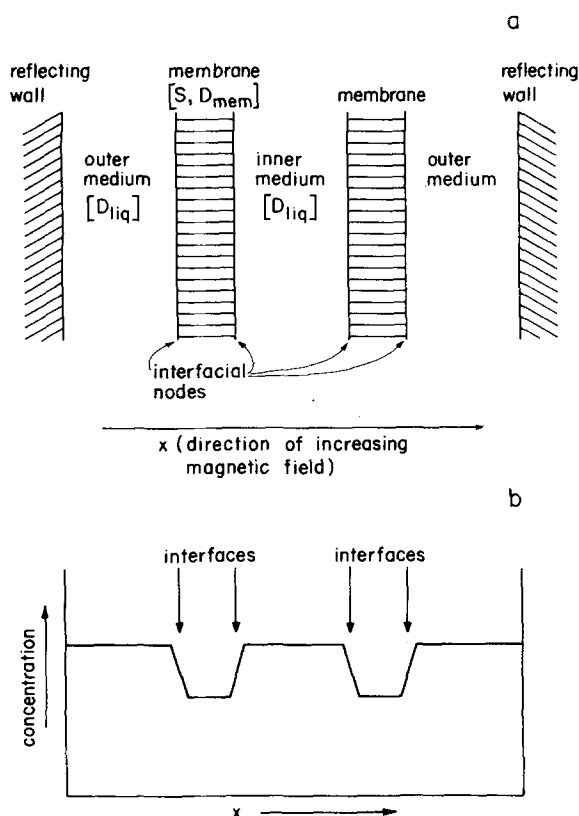


FIG. 3. (a) A bounded five region model system including inner and outer liquid media on either side of a membrane having a diffusion coefficient  $D_{mem}$  and solubility factor  $S$ . (b) A typical calculated concentration profile of the system in Fig. 3(a) where the spin-bearing species is less soluble in the membrane. In this specific example,  $\Delta\nu_{mem}^0/k_B T = 0.40$ ,  $N = 50$ , and interfaces are shown at  $i = 15, 20, 30$ , and  $35$ .

$$f(i) = \begin{cases} +(U/k_B T)\delta_{i,i}, & \text{if the membrane is to the left of the interface,} \\ -(U/k_B T)\delta_{i,i}, & \text{if the membrane is to the right, as in Fig. 1,} \end{cases} \quad (27)$$

and the value of  $(U/k_B T)$  may be different for each membrane. In the case pictured in Fig. 3(a), membranes are simulated by regions of space having unique diffusive properties and bounded by two permeable interfaces. Continuous diffusion through the membranes is assumed, while modifications due to facilitated transport can be made via Eq. (26) if desired, but are ignored in this elementary demonstration of the numerical method.

### C. The double step procedure

From Eqs. (23)–(27), one is able to construct the proper matrix equation (19) for the heterogeneous model being studied. However, the solution of Eq. (19) as a function of time is not computationally straightforward. Solutions of the SLE applied in other studies have utilized Laplace transform methods<sup>17</sup> or diagonalization methods<sup>18(a)</sup> to treat the time dependence. The Laplace transform technique is limited, since its main advantage

lies in the calculation of only the  $t \rightarrow \infty$  results, while diagonalization methods are conceptually simple but computationally demanding due to the requirement of the complete storage of all the eigenvalues and eigenvectors. An approximate iterative scheme, the “double step” method, has been developed<sup>26a</sup> to solve the SLE in the time domain for arbitrary sized spin-basis sets.

The double step method involves the use of a FD description of the spatial variable(s); thus, the problem may be expressed in the form of Eq. (19). This has the formal solution

$$\rho(t) = \exp[-i\Omega t + \mathbf{W}t] \rho(0), \quad (28)$$

which does not directly lead to a practical method of solution. However, over a short enough time span ( $\Delta t$ ), the nodal values in  $\rho$  do not vary appreciably from the internodal diffusion. During  $\Delta t$ , though, the values of spin-density matrix elements at each node will evolve due to the quantum mechanical interactions in Eq. (19). Therefore, on a very short time scale, the quantum and diffusion operators commute approximately and their effects may be separated. This can be more rigorously specified by the expansion of Eq. (28) to  $O[(\Delta t)^2]$ :

$$\rho(\Delta t) \cong [1 + (-i\Omega + \mathbf{W})\Delta t + \frac{1}{2}(-i\Omega + \mathbf{W})^2(\Delta t)^2] \rho(0), \quad (29)$$

which can be partially reformed as

$$\rho(t + \Delta t) \cong e^{-i\Omega \Delta t} [1 + \mathbf{W} \Delta t] \rho(t), \quad (30a)$$

where we have indicated the variation in  $\rho$  over any  $\Delta t$  interval and recognizing in Eq. (30a) that the omitted terms of  $O[(\Delta t)^2]$  are

$$\text{Error}\{O[(\Delta t)^2]\} = \{-i[\mathbf{W}, \Omega] + \mathbf{W}\mathbf{W}\} \frac{(\Delta t)^2}{2}. \quad (30b)$$

Equations (30) are eminently suitable for numerical computation as a two step procedure for each  $\Delta t$  interval in time:

$$\rho^*(t + \Delta t) = [1 + \mathbf{W} \Delta t] \rho(t), \quad (31a)$$

$$\rho(t + \Delta t) = \mathbf{T}^{-1} e^{-i\Omega \Delta t} \mathbf{T} \rho^*(t + \Delta t), \quad (31b)$$

where  $\Omega_d = \mathbf{T} \Omega \mathbf{T}^{-1}$  may be solved for once and only involves  $N$  ( $N$  = total number of nodes) diagonalizations of  $L^2 \times L^2$  ( $L$  = total number of spin states) symmetric matrices, each of which is a partitioned, uncoupled sub-matrix along the diagonal of  $\Omega$ .<sup>26b</sup>  $\rho(t)$  contains the known values of the spin-density matrix element nodal values either previously calculated or supplied in a defined initial condition  $\rho(0)$ . Equations (30) and (31) are not unique, and the reverse order of the operations, or an average of Eq. (30) and its analog with the reordered operations, can be utilized, but we have found Eq. (30) sufficient for the present problem.

The suitability of using Eqs. (31) in the solution of the SLE lies in the relatively small amount of information required to be in high-speed core during each  $\Delta t$  step and peripheral storage of results not immediately needed is possible. This allows the time dependent solutions of the SLE on small-core computers even if large spin basis sets are considered.<sup>27</sup> Equation (31a), which is written as an explicit<sup>19</sup> solution of the diffusion equation, requires  $\leq 5N$  storage locations during computation while Eq. (31b) requires only about  $L^2(L^2 + 3)$  locations.

The previous discussion emphasizes the applicability of the double step method to the general solution of the time dependent SLE. Because of Eq. (8), only one spin-density matrix element will be considered for the present spin-echo simulations. Equation (31b) then simplifies since  $\Omega$  is originally diagonal, as given by Eq. (23). Starting with a known initial condition  $\rho_{\beta\alpha}(0)$ , one can iteratively perform the steps of Eqs. (31) until  $\tau$ , the time of the  $\pi$  pulse, is reached. Then the instantaneous  $\pi$  pulse is simulated by the operation

$$\text{Re}[\rho_{\beta\alpha}(\tau, \text{ after } \pi \text{ pulse})] = -\text{Re}[\rho_{\beta\alpha}(\tau, \text{ before } \pi \text{ pulse})], \quad (32)$$

after which Eqs. (31) can be used to iteratively step through time until  $\tau=2$  when, analogous to Eq. (9), the echo amplitude can be calculated in FD terms by

$$F(2\tau) = \sum_{l=1}^N |\text{Re}[\rho_{\beta\alpha}(l, 2\tau)]| \Delta x. \quad (33)$$

The numerical scheme in Eqs. (31)–(33) is the same as that used earlier for the case of bounded homogeneous diffusion by Wayne<sup>7(b)</sup> although derived by alternate arguments. We can improve upon the accuracy of the explicit diffusion equation solution (31a) by substituting the unconditionally stable implicit Crank–Nicolson procedure.<sup>19</sup> The new form of the diffusion step in  $\Delta t$  then is

$$\rho^*(t + \Delta t) = [1 - \frac{1}{2}\mathbf{W}\Delta t]^{-1} [1 + \frac{1}{2}\mathbf{W}\Delta t] \rho(t), \quad (34)$$

which we have used. The requirement of the matrix inversion in Eq. (34) is not found to be time or storage consuming since  $[1 - \frac{1}{2}\mathbf{W}\Delta t]$  is tridiagonal and efficient inversion methods are known.<sup>28</sup>

### III. RESULTS

The analytic results of Robertson<sup>8</sup> for the spin-echo amplitudes obtained using a steady gradient  $(\pi/2)$ – $\pi$ –pulse sequence for spins diffusing in a homogeneous, bounded medium served as an initial determination of the accuracy of numerical results. Simulating the case Robertson studied where we used  $N \geq 50$  and  $\Delta t \leq 10^{-4}$ , we reproduced his values of the echo amplitude versus  $2\tau$  to within 0.1% error with computations done on a PDP 11/34 minicomputer.

Computations were performed using (1) the explicit FD scheme of Eq. (31a); (2) the Crank–Nicolson FD scheme of Eq. (34); (3) reversed order of steps, i.e., (I) Eq. (31b) then (II) Eq. (31a); (4) reversed order of steps, i.e., (I) Eq. (31b) then (II) Eq. (34); and (5) averaging of test number 2 and 4 results for each  $\Delta t$ . In each test case, identical results were obtained to within 0.1% deviation. Also, checks were run on systems containing membranes to guarantee that no artifacts of the calculation appeared in the results for the echo amplitudes. Membranes were shifted in position along the  $x$  axis in one test (but their size and physical properties kept constant) and in another case constant terms were added to the magnetic field. Neither perturbation caused significant deviations in the echo amplitudes, as expected. This indicates the accuracy of the double step method when applied to the solution of the SLE.

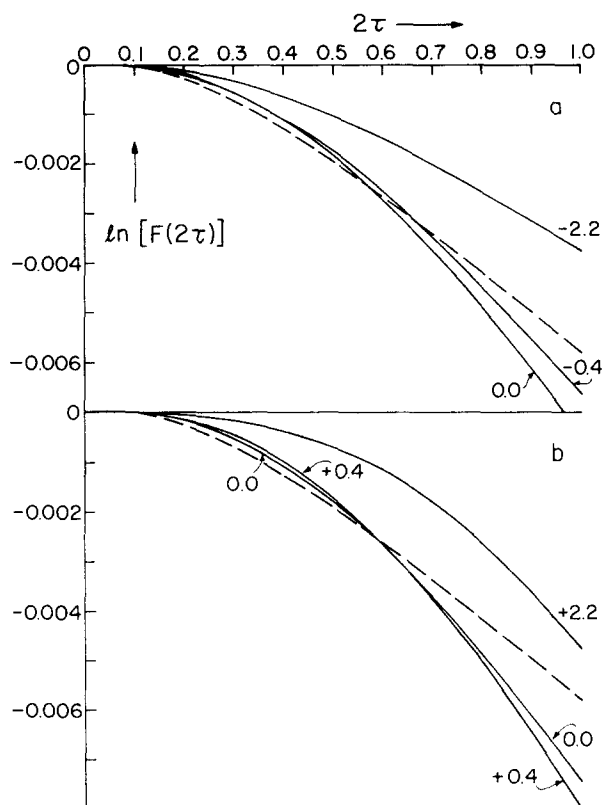


FIG. 4.  $\text{La}[F(2\tau)]$  calculated for the model system of Fig. 3 versus  $2\tau$  for various values of  $\Delta\mu_{\text{mem}}^0/k_B T$  as listed. Additional input includes  $T_2^{-1}=0$ ,  $\alpha=1$ ,  $D_{\text{mem}}/D_{11q}=1/4$ ,  $N=50$ ,  $\Delta t=10^{-4}$ , with an equilibrium initial condition. Interfaces are located at  $i=15, 20, 30$ , and  $35$ . Results in (a) refer to systems where the equilibrium spin concentration in the membrane ( $C_{\text{mem}}^{\text{eq}}$ ) is greater than or equal to that in the other media ( $C_{11q}^{\text{eq}}$ ). Results in (b) refer to cases where  $C_{11q}^{\text{eq}} \geq C_{\text{mem}}^{\text{eq}}$ . The dashed line in (a) and (b) displays the echo decay when there are no membranes present.

As mentioned above, we have studied in detail the case pictured in Fig. 3(a) which includes, in a simple example, all of the aspects of a heterogeneous system discussed in Sec. II (with facilitated transport neglected) and cannot be treated by analytic mathematical methods. Also included in the example studied was a variable initial condition. Figure 4 exhibits the logarithm of the spin-echo amplitude versus  $2\tau$  starting with the equilibrium system concentrations. In these cases, the pure diffusion of the spin-bearing particles (with the magnetic field off) is computed until equilibrium is attained (here about 0.1 to 0.5 time units), at which time (set as  $t=0$ ) the spin-echo experiment is simulated. The equilibrium concentration profile of our example for one typical value of  $S$  is seen in Fig. 3(b). Other profiles vary similarly and can be generated by the information given in Fig. 2. Figure 5 shows the simulated results for a spin-echo experiment where the solute was initially constrained to be within the inner medium of Fig. 3(a).<sup>29</sup>

The results in Figs. 4 and 5 are shown to vary with  $\Delta\mu_{\text{mem}}^0/k_B T$  (or  $S$ ) as one might predict. The functional dependence of the echo amplitude on time, as seen in Fig. 4, is significantly different in the cases where membranes are present than when they are absent (Fig.

4 dashed curve), since the spin-bearing molecules in the sample reveal the effects of movement in regions of different diffusivity. This is true even if membrane solubility effects are ignored, i. e., when  $\mu_{\text{mem}}^0/k_B T = 0.0$ . We show in Fig. 6 the effect of the variation of  $D_{\text{mem}}/D_{11q}$  on  $\ln[F(2\tau)]$ , utilizing an equilibrium initial condition of solute particles and a value of  $\Delta\mu_{\text{mem}}^0/k_B T = 0.4$  (i. e.,  $C_{11q}/C_{\text{mem}} = 1.5$ ).

Figure 5 exhibits the results for echo amplitudes obtained when the spin-bearing species was initially uniformly concentrated between (but not in) the two membranes. Since it takes, for the system parameters used in this study, until  $t=0.1$  or  $0.2$  to attain the equilibrium distribution, the curves of Fig. 5 resemble those of Fig. 4 except that they are displaced along the time axis.

The echo amplitudes obtained using other pulse sequences (i. e., Carr-Purcell<sup>4</sup> type experiments) or utilizing pulsed gradients<sup>5</sup> have been obtained by us<sup>30</sup> by applying our numerical method with straightforward modifications.

#### IV. CONCLUSIONS

A numerical method for the calculation of NMR spin-echo amplitudes in heterogeneous, bounded media has been presented. This double step method is discussed

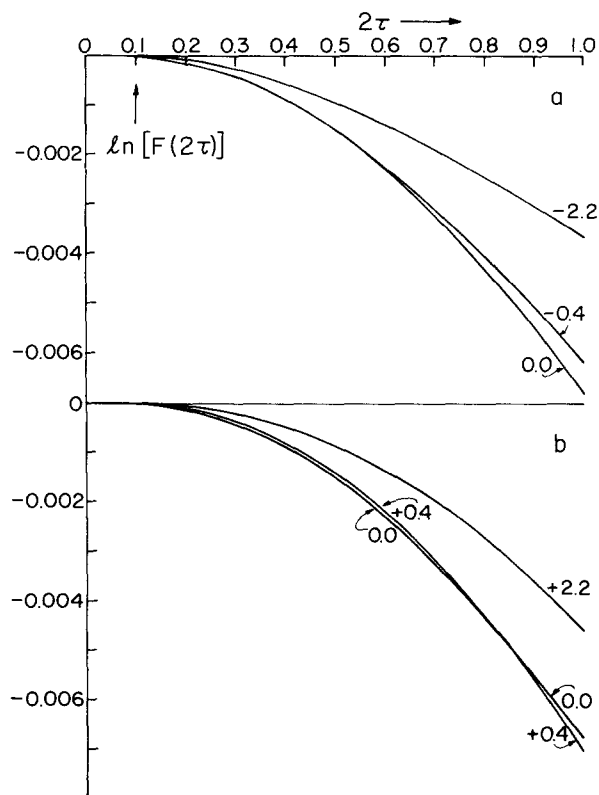


FIG. 5.  $\ln[F(2\tau)]$  calculated for the model system of Fig. 3 versus  $2\tau$  for several values of  $\Delta\mu_{\text{mem}}^0/k_B T$  as noted. Additional program input includes  $T_2^{-1}=0$ ,  $\alpha=1$ ,  $D_{\text{mem}}/D_{11q}=1/4$ ,  $N=50$ ,  $\Delta t=10^{-4}$ , with a membrane enclosed initial condition (i. e., all spins in the inner medium of Fig. 3). Interfaces are located at  $i=15, 20, 30$ , and  $35$ . Results given for (a) systems with  $C_{11q}^{\text{eq}} \leq C_{\text{mem}}^{\text{eq}}$  and (b)  $C_{11q}^{\text{eq}} \geq C_{\text{mem}}^{\text{eq}}$ .

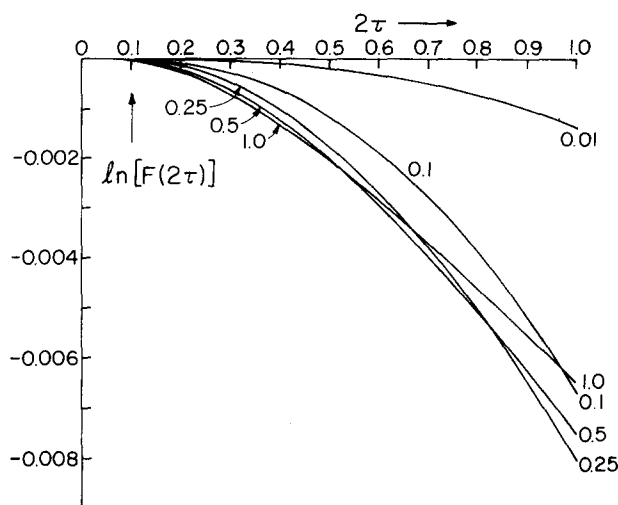


FIG. 6.  $\ln[F(2\tau)]$  calculated for the model system of Fig. 3 versus  $2\tau$  for various values of  $D_{\text{mem}}/D_{11q}$  as listed. Additional input includes  $T_2^{-1}=0$ ,  $\alpha=1$ ,  $N=50$ ,  $\Delta t=10^{-4}$ ,  $\Delta\mu_{\text{mem}}^0/k_B T=0.4$ , and an equilibrium initial condition. Interfaces are located at  $i=15, 20, 30$ , and  $35$ .

in general terms as a computationally viable scheme for the solution of the time-dependent SLE. Within this FD format, the inclusion of spatial regions with different physical properties in a system is accomplished by a detailed FD analysis leading to the appropriate transition matrix elements. These matrix elements include the effects of a spatially varying diffusion coefficient and solubility, arising from the use of an interface separating regions with different intrinsic chemical potential  $\Delta\mu_{\text{mem}}^0$ .

It is clear in the light of the study by Tanner<sup>15</sup> that significant difficulties arise in the attempt to derive useful physical data from spin-echo results from heterogeneous systems. The pathway suggested by earlier studies<sup>7,12,15</sup> concentrates on the fitting of the logarithm of amplitude values to a formula linear in  $D$  [or  $D(t)$ ]. However, the relationship of such a  $D(t)$  to a specific microscopic model is not at all clear in general (and may not even be unique). Thus, it is important to explicitly relate an appropriate microscopic model to the observations, and this is made feasible by our approach.

The direct simulation method described by this study will also present difficulties in an analysis of experimental data. However, as discussed in Sec. I, if the experiments are run under controlled biological and physical circumstances, and all relevant known information about the system is inserted in the analysis, then the numerical modeling approach outlined above could prove to be a useful probe of the microscopic effects influencing the observed spin-echo results, such as membrane studies in heterogeneous but structured systems.

#### ACKNOWLEDGMENTS

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- <sup>1</sup>E. L. Hahn, *Phys. Rev.* **80**, 580 (1950).
- <sup>2</sup>For elementary discussions, see D. C. Hauessen and T. D. Bonifield, *Am. J. Phys.* **43**, 824 (1975); T. C. Farrar and E. D. Becker, *Pulse and Fourier Transform NMR* (Academic, New York, 1971).
- <sup>3</sup>H. C. Torrey, *Phys. Rev.* **104**, 563 (1956).
- <sup>4</sup>H. Y. Carr and E. M. Purcell, *Phys. Rev.* **94**, 630 (1954).
- <sup>5</sup>E. O. Stejskal and J. E. Tanner, *J. Chem. Phys.* **42**, 288 (1965).
- <sup>6</sup>E. O. Stejskal, *J. Chem. Phys.* **43**, 3597 (1965).
- <sup>7</sup>(a) R. C. Wayne and R. M. Cotts, *Phys. Rev.* **151**, 264 (1966); (b) R. C. Wayne, Ph.D. thesis, Cornell University, 1966.
- <sup>8</sup>B. Robertson, *Phys. Rev.* **151**, 273 (1966).
- <sup>9</sup>C. H. Neuman, *J. Chem. Phys.* **60**, 4508 (1974).
- <sup>10</sup>J. E. Tanner and E. O. Stejskal, *J. Chem. Phys.* **49**, 1768 (1968).
- <sup>11</sup>R. L. Cooper *et al.*, *Biophys.* **14**, 161 (1974).
- <sup>12</sup>D. G. Stout and R. M. Cotts, in ACS Symposium Series No. 34, *Magnetic Resonance in Colloid and Interface Science*, edited by H. A. Resing and C. G. Wade (American Chemical Society, New York, 1976).
- <sup>13</sup>F. F. Brown, I. Campbell, *et al.*, *FEBS Lett.* **82**, 12 (1977).
- <sup>14</sup>M. Eddin, *Annu. Rev. Biophys. Bioeng.* **3**, 179 (1974).
- <sup>15</sup>J. E. Tanner, *J. Chem. Phys.* **69**, 1748 (1978).
- <sup>16</sup>A density matrix approach was utilized by Robertson (Ref. 8), but the chosen basis functions were the spatially dependent expansion functions of  $M(x, t)$  rather than the simple spin eigenfunctions, which are used here.
- <sup>17</sup>Other applications of numerical solutions of the SLE to magnetic resonance topics are discussed in J. H. Freed and J. B. Pedersen, *Adv. Magn. Reson.* **8**, 1 (1976); G. P. Zientara and J. H. Freed, *J. Chem. Phys.* **70**, 2587 (1979); and *Electron Spin Relaxation in Liquids*, edited by L. Muus (Plenum, New York, 1972).
- <sup>18</sup>Several examples are (a) L. P. Hwang and J. H. Freed, *J. Chem. Phys.* **63**, 4017 (1975); (b) Z. Schulten and K. Schulten, *J. Chem. Phys.* **66**, 4616 (1977); (c) H. Werner, Z. Schulten, and K. Schulten, *J. Chem. Phys.* **67**, 646 (1977).
- <sup>19</sup>R. Richtmyer and K. Morton, *Difference Methods for Initial-Value Problems* (Interscience, New York, 1967), 2nd edition.
- <sup>20</sup>An FD scheme involving variable nodal separations is discussed in G. P. Zientara and J. H. Freed, *J. Chem. Phys.* **70**, 1359 (1979).
- <sup>21</sup>J. F. Danielli, in *Surface Phenomena in Chemistry and Biology*, edited by J. F. Danielli, K. G. Parkhurst, and A. C. Riddiford (Pergamon, New York, 1958); energy barrier models were recently reviewed in L. F. DelCastillo, E. A. Mason, and L. A. Viehland, *Biophys. Chem.* **9**, 111 (1979).
- <sup>22</sup>Diffusion through interfaces is discussed in (a) E. Scott, L. Tung, and H. Drickamer, *J. Chem. Phys.* **19**, 1075 (1951); (b) J. T. Davies and J. B. Wiggill, *Proc. R. Soc. (London) Ser. A* **525**, 277 (1960); (c) J. T. Davies and E. K. Rideal, *Interfacial Phenomena* (Academic, New York, 1961).
- <sup>23</sup>More explicitly, if  $\rho$  contains nodal values of  $L^2 > 1$  spin-density matrix elements, then we would employ the supermatrix  $\mathbf{W}'$  (cf. Freed and Pedersen, Ref. 17) which is formed by multiplying each element of  $\mathbf{W}$  by an  $L^2 \times L^2$  unit matrix. In the examples of this study,  $L = 1$  by virtue of Eqs. (8); hence,  $\mathbf{W}$  has been used in Eq. (19).
- <sup>24</sup>These probabilities are linked to an explicit FD solution of Eq. (19) in time (cf. Ref. 19).
- <sup>25</sup>See, for example, the elementary discussion in R. Dyson, *Essentials of Cell Biology* (Allyn and Bacon, Boston, 1978), 2nd edition. Dyson illustrates the three pathways presently believed in operation in different cases: (1) binding (of particles to a large biomolecule) and translocation (linked particle-protein movement through membrane to opposite face); (2) binding, translocation, and release (into medium on other membrane side); or (3) channeling (particle movement through membrane "opening" or "channel").
- <sup>26</sup>(a) This method was previously reported by J. H. Freed, in *Chemically Induced Magnetic Polarization: Theory, Technique, and Applications*, edited by L. T. Muus, P. W. Atkins, K. A. McLauchlan, and J. B. Pedersen (Reidel, Dordrecht, 1977); (b) Actually, it is sufficient, when the diagonalization of  $\Omega$  is solely determined by  $\mathcal{K}^\alpha$ , to merely diagonalize  $\mathcal{K}$  in each  $L$ -dimensional spin space for each node, since  $\mathcal{K}^\alpha$  given by Eq. (5) is then diagonal in the  $L^2$  Liouville spin space, (cf. Ref. 17).
- <sup>27</sup>The strategy of the double step method is applicable to other areas of study concerned with solutions of partial differential equations with terms that cause variation in the solution according to time scales of different magnitudes. For example, see M. Okamoto and T. Amano, *J. Comp. Phys.* **26**, 80 (1978).
- <sup>28</sup>Reference 19, p. 198.
- <sup>29</sup>This is similar to the initial condition used by Tanner in Ref. 15.
- <sup>30</sup>R. Wayne [Ref. 7(b)] also obtained numerical results for different pulse sequences, etc., in treating models of a homogeneous medium.