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Monte Carlo simulation of diffusion in a spatially nonhomogeneous medium: correction to the Gaussian steplength ☆

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Abstract

Monte Carlo (MC) simulation of diffusion processes has proved to be a powerful and valuable adjunct to deterministic solutions of the diffusion equation. For the case of a constant diffusion coefficient it is well established that a MC method using a steplength chosen from the appropriate Gaussian distribution gives accurate results. However, in the case where the diffusion coefficient is spatially dependent, straightforward modification of this method, involving replacing the constant diffusion coefficient by the spatially dependent one in the steplength formula, leads to a systematic error, as shown by comparing MC averages with deterministic solutions. Furthermore, reducing the timestep, and hence the average steplength, does not reduce this error. In this paper, we trace the source of the error and provide a simple and readily calculated correction to the Gaussian steplength that reconciles the MC and deterministic approaches.

Keywords: Monte Carlo; Diffusion; Stochastic modelling; Gaussian distribution

1. Introduction

Monte Carlo (MC) simulation has proved a valuable tool for investigating processes involving the diffusion of substances. In particular, in has been used in neurophysiology to study the action of neurotransmitters [2–5,9,16] and more recently the function of calcium ions (Ca^{2+}) in initiating and modifying synaptic function [6,7,10,14].

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The MC method simulates the dynamics of each particle; in a short time interval Δt a particle is moved from the point with cartesian coordinates (x, y, z) to a neighbouring point with coordinates $(x + \Delta x,\ y + \Delta y,\ z + \Delta z)$, where the random increments Δx, Δy and Δz are chosen from a suitable distribution. For the case of a constant diffusion coefficient $D = D_0$ this distribution is Gaussian and the increments are readily generated numerically according to the formula $\Delta x = \sqrt{2D_0\Delta t}\zeta$ (with similar formulas for Δy and Δz), where ζ is a standard normal deviate, that is, a number randomly chosen from a Gaussian distribution with mean 0 and standard deviation 1.

Advantages of the MC method for neurobiological modelling include the ability to deal with complicated geometries, the realistic treatment of the binding of ions and molecules to receptors and the explicit demonstration of the extent of stochastic variability in observable quantities, this latter aspect being a major feature of experimental records. A disadvantage of the MC method is that often many runs are needed in order to average out these variations and obtain reliable mean values. Mean values can be directly obtained from solutions of the partial differential equation for diffusion and this can form a useful check and supplement to the MC method.

In biological applications the diffusion coefficient has to be modified, for a number of reasons, from the value it would have in water. One modification reduces the value of D uniformly in order to approximate the effects of buffering agents [17]; another reduces the value, again uniformly, in order to allow for the effects of obstructions to free diffusion. This latter consideration leads to the idea of tortuosity, where the diffusion coefficient is modified to an effective coefficient $D^* = D_0/\lambda^2$, where the constant λ is a measure of the tortuosity [13]. The MC method is still immediately applicable to these cases, provided D_0 is replaced by its appropriate value in the formula for the stepsize Δx.

In a more general case, one may have a diffusion coefficient that varies with distance. A particular case is that of Ca^{2+} diffusion inside the neuromuscular junction of the crayfish; here it was found that in order to account for certain experimental results it was necessary to assume that the tortuosity decreases as one moves away from the release site and in fact that there is a fivefold increase in the diffusion coefficient over a distance of the order of 100 nm [12]. Here, the calculations were done using a deterministic model and involved solving differential equations with appropriate boundary conditions. In attempting to reproduce these calculations using the MC approach we found that there was a systematic deviation of the MC average from the deterministic result. In applying the MC method, we calculated the stepsize for position x using $\Delta x = \sqrt{2D(x)\Delta t}\zeta$, where $D(x)$ is now the spatially dependent diffusion coefficient, as this seemed to be the obvious extension of the constant diffusion coefficient case. The puzzling feature was that the error did not decrease when the timestep Δt was reduced, even to very small values.

This discrepancy led us to do a systematic comparison of MC and deterministic results for spatially dependent diffusion coefficients, working in one dimension for simplicity and starting with the case of linear spatial dependence, where an exact solution is available. We found that although the exact distribution for the stepsize differed only slightly from a Gaussian distribution, nevertheless the difference was important because it is biased in one direction and thus accumulates over time. Furthermore, the error resulting from using the Gaussian steplength was, to first order, proportional to the timestep Δt, which explained why reducing the timestep did not help: halving Δt did indeed halve the error but since twice as many steps were now required there was no overall improvement in accuracy.

Accurate MC results could be obtained by using the exact distribution for the stepsize, but this is cumbersome and moreover an analytic expression for the exact distribution is available only for a few special cases. Thus we looked for an easily computable correction to the Gaussian steplength that would be applicable in the general case. This paper presents the formula for such a correction and demonstrates that it reconciles the MC and deterministic approaches both for the case of a linearly varying diffusion coefficient and for the general case.

2. Diffusion

2.1. Homogeneous case

The general equation for diffusion in one dimension is

$$\frac{\partial c}{\partial t} = \frac{\partial}{\partial x}\left(D\frac{\partial c}{\partial x}\right), \tag{1}$$

where $c \equiv c(x,t)$ is the concentration of the diffusing substance and $D = D(x,t)$ is the diffusion coefficient. In the case where D is constant, $D = D_0$, Eq. (1) reduces to

$$\frac{\partial c}{\partial t} = D_0\frac{\partial^2 c}{\partial x^2}. \tag{2}$$

For an instantaneous source of strength c_0 at $x = x_0$ and time $t = 0$, that is,

$$c(x,0) = c_0\delta(x - x_0), \tag{3}$$

this has solution

$$c(x,t) = \frac{c_0}{\sqrt{4\pi D_0 t}}\mathrm{e}^{-(x-x_0)^2/4D_0t}. \tag{4}$$

An alternative interpretation of Eq. (4) is that

$$f_X(x) = \frac{1}{\sqrt{4\pi D_0 t}}\mathrm{e}^{-x^2/4D_0t} \tag{5}$$

is the probability distribution for finding a particle at location x at time t, given that it was released from the origin at time $t = 0$. This is just the distribution function for a Gaussian random variable with mean $\mu = 0$ and standard deviation $\sigma = \sqrt{2D_0t}$.

The above contains the basis of the MC method for simulating the diffusion of a particle. One chooses some small time interval Δt and then moves the particle a random distance $X(\Delta t)$, where $X(t)$ is a random variable with distribution given by Eq. (5). The random distance Δx that the particle moves in time Δt can then be computed as

$$\Delta x = \sqrt{2D_0\Delta t}\zeta, \tag{6}$$

where ζ is a standard normal deviate. An alternative expression is

$$\Delta x = \sqrt{4D_0\Delta t}\,\mathrm{erf}^{-1}(2q - 1), \tag{7}$$

where $\mathrm{erf}(z) = (2/\sqrt{\pi})\int_0^z \exp(-x^2)\,\mathrm{d}x$ and q is a random deviate uniformly distributed on [0, 1]. In practice one can choose a suitably fine mesh for q (for example, divide the interval [0, 1] into 100 equal intervals) and construct a table of values of $\mathrm{erf}^{-1}(2q - 1)$; the Monte Carlo simulation is then implemented by choosing at random a value from this table, multiplying it by the constant factor $\sqrt{4D_0\Delta t}$ to get Δx and moving the particle to the new position $x + \Delta x$. This process is then repeated as often as necessary in order to generate the random walk executed by a particle.

In the particular application of interest to us, calcium ions are released from a point source as the result of a train of action potentials arriving at that location, with each impulse resulting in release [6,7,10,12]. These ions then diffuse independently through the surrounding medium and act on receptors

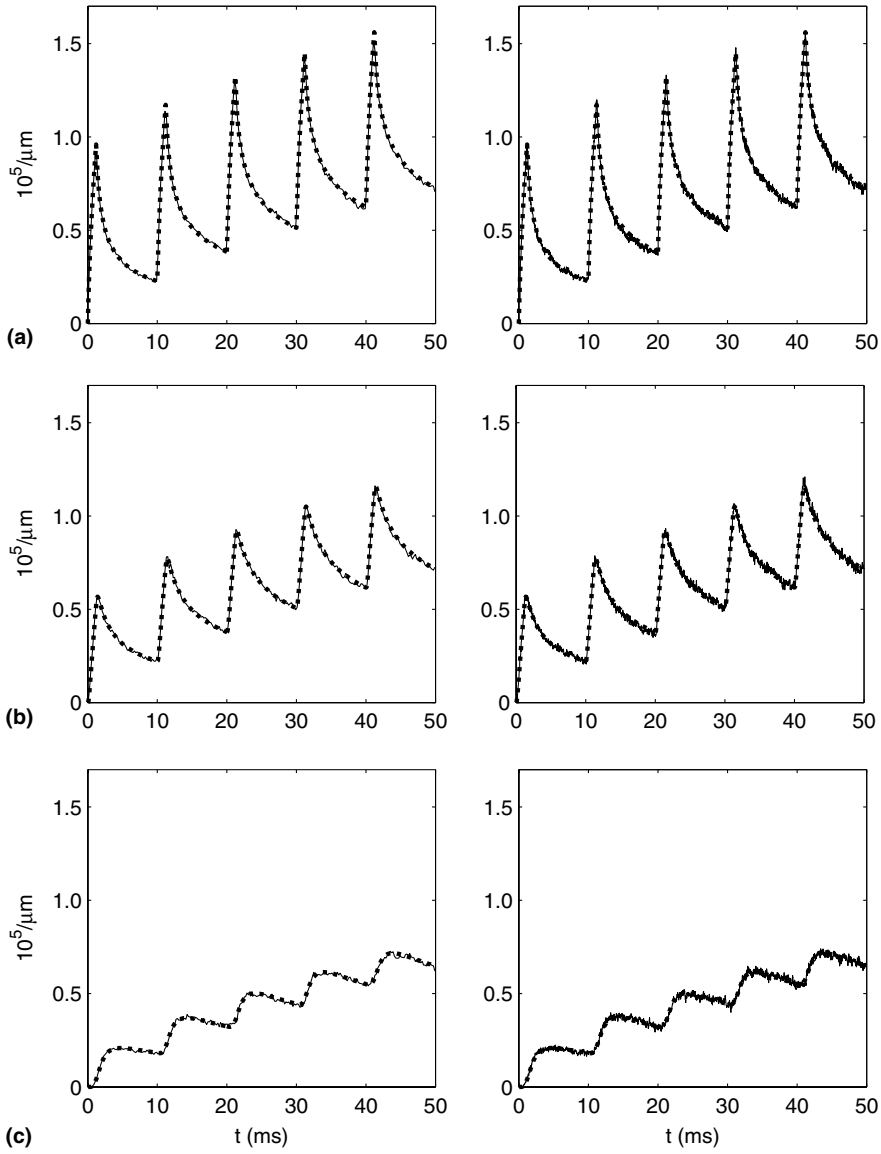

Fig. 1. Comparison of MC and deterministic results for the case of a constant diffusion coefficient, D_0. A 100 Hz train of action potentials results in the point release of calcium ions, with 7776 ions released over the 1.2 ms following the arrival of each impulse (corresponding to a Ca^{2+} current of 1.08×10^{-20} mol ms^{-1}). These ions diffuse, in one dimension, and the resulting time course of the concentration at distances from the release site of 20, 60 and 180 nm is shown in (a), (b) and (c), respectively. The concentration is expressed as the number of particles, scaled by 10^5 per μm. The solid line gives the MC result and the broken line the deterministic result obtained by solving the diffusion equation. The value of the diffusion coefficient, corrected for buffering, was $D_0 = 4$ μm^2 s^{-1} and the timestep used was $\Delta t = 0.15$ μs. The resulting concentration, in the MC case, was calculated by averaging the particle count over a 20 nm length and a 200 μs time period (left column) or 20 μs time period (right column). Averaging over the longer time period smoothes the results so as to make comparison with the deterministic results clearer, without changing the overall shape of the MC curves; hence the 200 μs averaging has been used for the other graphs in this paper.

at varying distances from the release site. Fig. 1 shows a one-dimensional version of the process for the case of a constant diffusion coefficient and a 100 Hz train of action potentials; panels (a), (b) and (c) show the Ca^{2+} concentration at distance of 20, 60 and 180 nm, respectively, from the source, with the

solid line giving the MC result and the broken line the deterministic result obtained by solving the one-dimensional diffusion equation, Eq. (1). It is clear that the MC average agrees closely with the deterministic result.

2.2. Nonhomogeneous case

Now suppose the diffusion coefficient depends on position, $D \equiv D(x)$. The naïve approach to MC simulation in this case is to simply replace D_0 by $D(x)$ in Eq. (6); that is, in time Δt the particle moves from x to $x + \Delta x$, where the steplength Δx is now to be computed as

$$\Delta x = \sqrt{2D(x)\Delta t}\zeta. \tag{8}$$

However, this turns out to introduce a significant systematic error and this error does not decrease when the timestep Δt is reduced, even to very small values. This is illustrated in Fig. 2, where the calculation of Fig. 1 is repeated, only now the diffusion coefficient depends on distance. Specifically [12] (see also the web site http://mrb.niddk.nih.gov/matveev),

$$D(x) = \widehat{D}[1 - 0.8u(x)], \tag{9}$$

where

$$u(x) = \frac{1}{2}\{\tanh[A(b - x)] + 1\} \tag{10}$$

and $\widehat{D}$ is a constant. There is now considerable deviation between the MC (solid line) and the deterministic (broken line) results, these differences becoming larger with increasing time. Reduction of the timestep by a factor of 10 (right-hand column) does not improve the accuracy of the MC results.

One way around this problem would be to use the exact distribution resulting from the spatially dependent diffusion coefficient $D(x)$, but there are two drawbacks here: the first is that an analytic expression for the probability distribution is only known for a limited number of special cases; the second is that the distribution will depend in a non-trivial way on x and consequently it will have to be re-sampled at each spatial point of the particle's trajectory; no simple formula analogous to Eqs. (6) or (7), where the sampling is done from a fixed Gaussian distribution, will be available.

2.3. Correction to Gaussian steplength

Let $f_X(x)$ be the Gaussian distribution function as given by Eq. (5). Then if Δx is the steplength chosen from this distribution, it is related to a uniform random deviate q by

$$q = \int_{-\infty}^{\Delta x} f_X(x)\,\mathrm{d}x. \tag{11}$$

Similarly, if $f_W(w)$ is the distribution function for the exact steplength Δw, then

$$q = \int_{-\infty}^{\Delta w} f_W(w)\,\mathrm{d}w. \tag{12}$$

We wish to find an expression for the correction, ϵ, to the Gaussian steplength:

$$\Delta w = \Delta x + \epsilon, \tag{13}$$

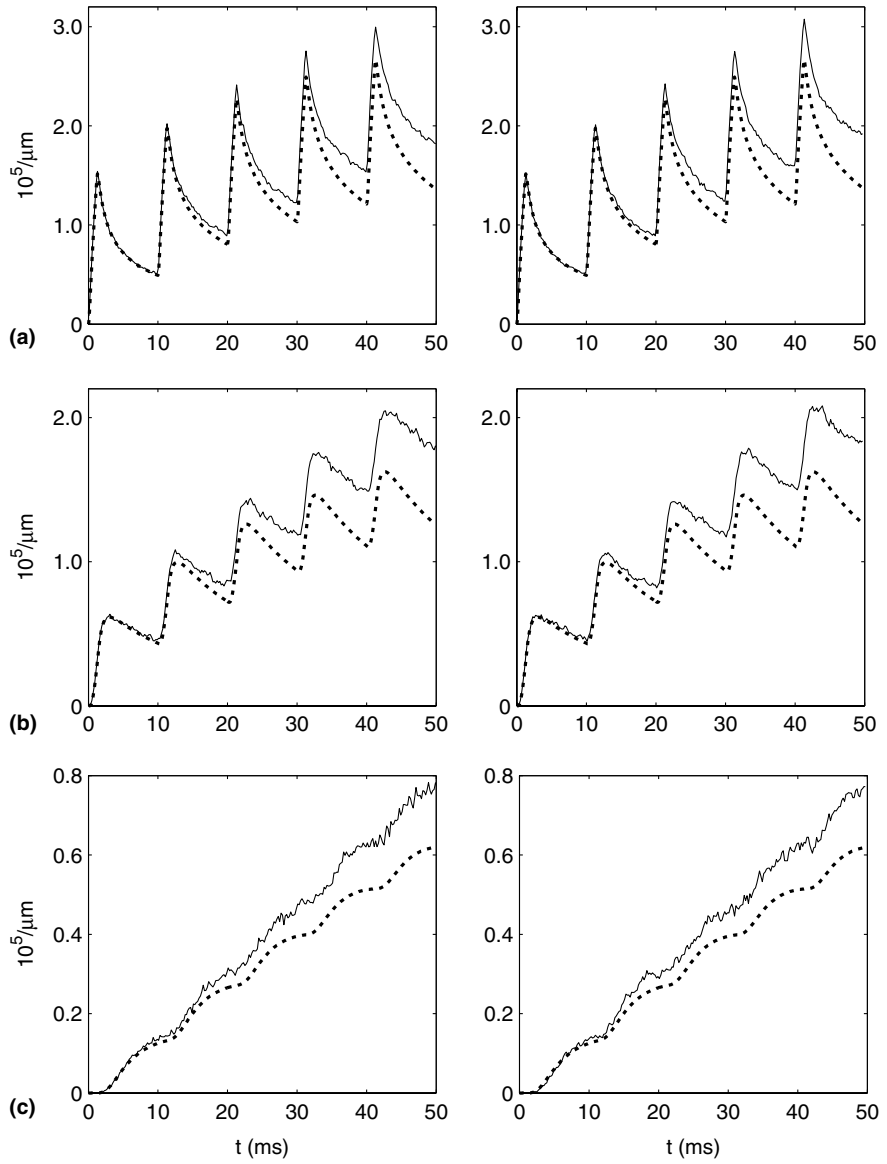

Fig. 2. Comparison of MC and deterministic results for the case of a variable diffusion coefficient, $D(x)$, as given by Eqs. (9) and (10), with $\widehat{D} = 4\ \mu m^2\ s^{-1}$, $A = 35\ \mu m^{-1}$ and $b = 0.2\ \mu m$, giving a diffusion coefficient that increases in magnitude approximately fivefold in the region 100 nm $\lesssim x \lesssim$ 300 nm. The remaining details are as for Fig. 1, except that the left column uses a timestep Δt of 0.15 μs and the right column a reduced timestep of 0.015 μs.

where Δx is to be calculated using Eq. (8). From Eqs. (11) and (12),

$$\int_{-\infty}^{\Delta x} f_X(x)\,\mathrm{d}x = \int_{-\infty}^{\Delta x} f_W(w)\,\mathrm{d}w + \int_{\Delta x}^{\Delta x+\epsilon} f_W(w)\,\mathrm{d}w, \tag{14}$$

$$= \int_{-\infty}^{\Delta x} f_W(w)\,\mathrm{d}w + \epsilon f_W(\Delta x) + \mathcal{O}(\epsilon^2), \tag{15}$$

and thus to first order,

$$\epsilon = \frac{\int_{-\infty}^{\Delta x} f_X(x)\,\mathrm{d}x - \int_{-\infty}^{\Delta x} f_W(w)\,\mathrm{d}w}{f_W(\Delta x)}. \tag{16}$$

This gives the required correction to the steplength; however, it is not computationally convenient, since it requires the evaluation of integrals and re-calculation for each choice of Δx. Below we show that this expression can be considerably simplified.

2.4. Linearly varying diffusion coefficient

Consider the case where the diffusion coefficient is a linear function of position:

$$D(x) = D_0(1 + \alpha x), \tag{17}$$

where D_0 and α are constants. Then the solution of (1) under the boundary condition (3) is

$$c(x,t) = \frac{c_0}{D_0|\alpha|t}\mathrm{e}^{-(y^2+y_0^2)/D_0\alpha^2 t} I_0\left(\frac{2yy_0}{D_0\alpha^2 t}\right), \tag{18}$$

where $y = \sqrt{1+\alpha x}$, $y_0 = \sqrt{1+\alpha x_0}$ and $I_0(\cdot)$ is a modified Bessel function. This expression follows from the temperature distribution resulting from an instantaneous cylindrical heat source [8, Section 10.3]; we also give a direct derivation in Appendix A. In the limit $\alpha \to 0$ Eq. (18) reduces to the usual Gaussian distribution, Eq. (4).

It follows from Eq. (18) that the exact distribution for the case of a linearly varying diffusion coefficient, Eq. (17), is

$$f_W(w) = \frac{1}{D_0|\alpha|t}\mathrm{e}^{-(2+\alpha w)/D_0\alpha^2 t} I_0\left(\frac{2\sqrt{1+\alpha w}}{D_0\alpha^2 t}\right). \tag{19}$$

We wish to expand this about the corresponding Gaussian distribution for the case where w and t are small, with $w = \mathcal{O}(t^{1/2})$ (since $\Delta x = \mathcal{O}(\sqrt{\Delta t})$. The result is (see Appendix A)

$$f_W(w) = \frac{1}{\sqrt{4\pi D_0 t}}\mathrm{e}^{-w^2/4D_0 t}\left(1 - \frac{\alpha}{4}w + \frac{\alpha}{8}\frac{1}{D_0 t}w^3 + \mathcal{O}(w^2)\right). \tag{20}$$

Substituting this into Eq. (16) and doing the integrals leads to

$$\epsilon \approx \epsilon_1 = \frac{\frac{\alpha}{2}D_0\Delta t + \frac{\alpha}{4}(\Delta x)^2}{1 - \frac{\alpha}{4}\Delta x + \frac{\alpha}{8D_0\Delta t}(\Delta x)^3}. \tag{21}$$

This gives an easily evaluated expression for the correction to the Gaussian steplength. Note that this gives the correction for going from $x = 0$ to $x = \Delta x$; if we start from $x = x_0$ then D_0 should be replaced by the value of $D(x)$ at the beginning of this step, that is, by $D_0(1 + \alpha x_0)$ and of course Δx should be computed using Eq. (6) with the same replacement for D_0. In deriving Eq. (21) only the leading terms have been kept; the next higher order correction, ϵ_2, is given in Appendix A, Eq. (A.16), and again only involves simple algebraic operations for its computation. Fig. 3 shows the relative magnitude of these corrections as functions of Δx for several values of α. Figs 3(a) and (b) show that even for a large value of α (100 $\mu\mathrm{m}^{-1}$) there is only a slight difference between the Gaussian distribution and the distribution obtained using a linearly varying diffusion coefficient. Fig. 3(C) gives the steplength corrections ϵ, ϵ_1 and ϵ_2 for the case where $\alpha = 1.4$ $\mu\mathrm{m}^{-1}$; it is clear that over the relevant range of Δx (the Gaussian distribution for Δx is shown as a dot-dashed line) ϵ_1 is sufficiently accurate. Even for the larger value $\alpha = 20$ $\mu\mathrm{m}^{-1}$ Fig. 3(d) shows that ϵ_1 is still accurate except near the tails of the Δx distribution.

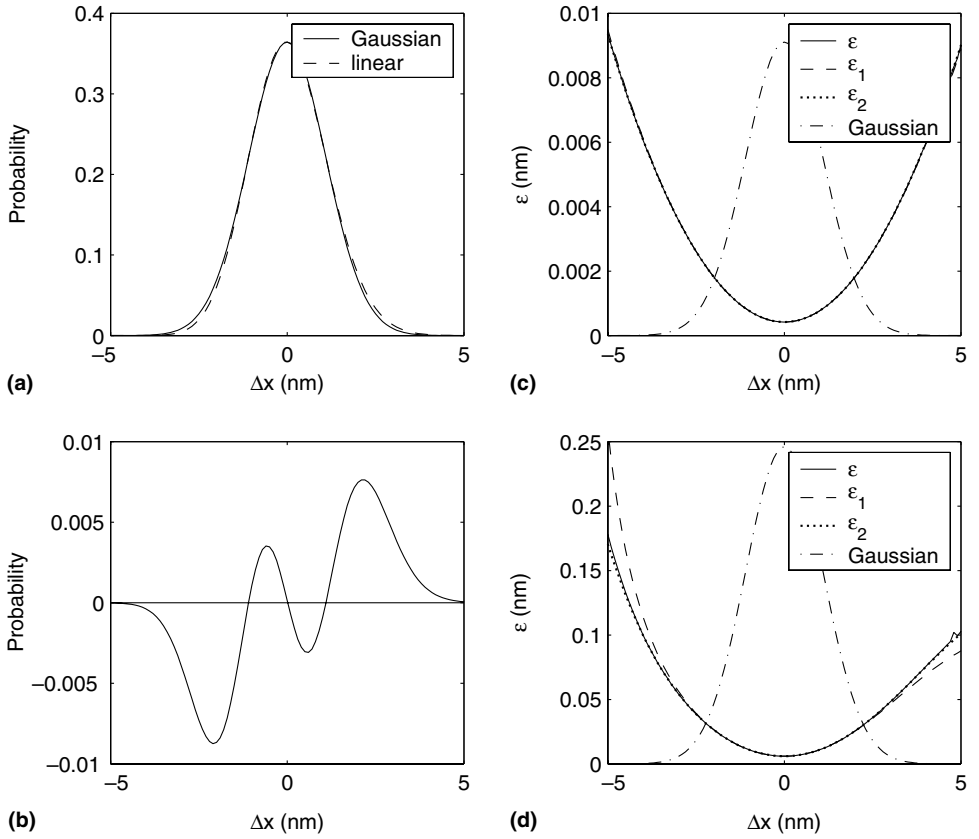

Fig. 3. Corrections to the steplength for the case of the linearly varying diffusion coefficient $D(x)$ given by Eq. (17). (a) shows the Gaussian probability distribution (solid line) and the distribution obtained for a linearly varying diffusion coefficient (broken line) as functions of the steplength Δx, for the case where $\alpha = 100\ \mu m^{-1}$. The Gaussian density is given by Eq. (5) with $x = \Delta x$ and $t = \Delta t$; the linear density is given by Eq. (19) with $w = \Delta x$ and $t = \Delta t$. (b) shows the difference (linear – Gaussian) between the two distributions in (a). (c) shows various approximations to the correction of the steplength for the case where $\alpha = 1.4\ \mu m^{-1}$. Shown are: ϵ as given by Eq. (16) (solid line), ϵ_1 as given by Eq. (21) (broken line) and ϵ_2 as given by Eq. (A.16) (dotted line). Also shown is the (scaled) Gaussian distribution for the steplength Δx (dot-dashed line). (d) repeats (c) for the case where $\alpha = 20\ \mu m^{-1}$. In all cases, the remaining parameters were $D_0 = 4\ \mu m^2\ s^{-1}$ and $\Delta t = 0.15\ \mu s$.

Fig. 4 shows the results of Ca^{2+} diffusion, with the same release protocol as in Fig. 1, but with a linearly varying diffusion coefficient given by Eq. (17) with the left column giving the results using the uncorrected steplength and the right column giving the results when the leading correction ϵ_1 is used. Again, the uncorrected steplength leads to a systematic and increasing error (compare Fig. 2), but the corrected case gives good agreement with the deterministic result.

2.5. General non-homogeneous case

In the general case we use a linear approximation to $D(x)$ at each step. Now

$$D(x_0 + \Delta x) = D(x_0)\left(1 + \frac{D'(x_0)}{D(x_0)}\Delta x\right) + \mathcal{O}[(\Delta x)^2], \tag{22}$$

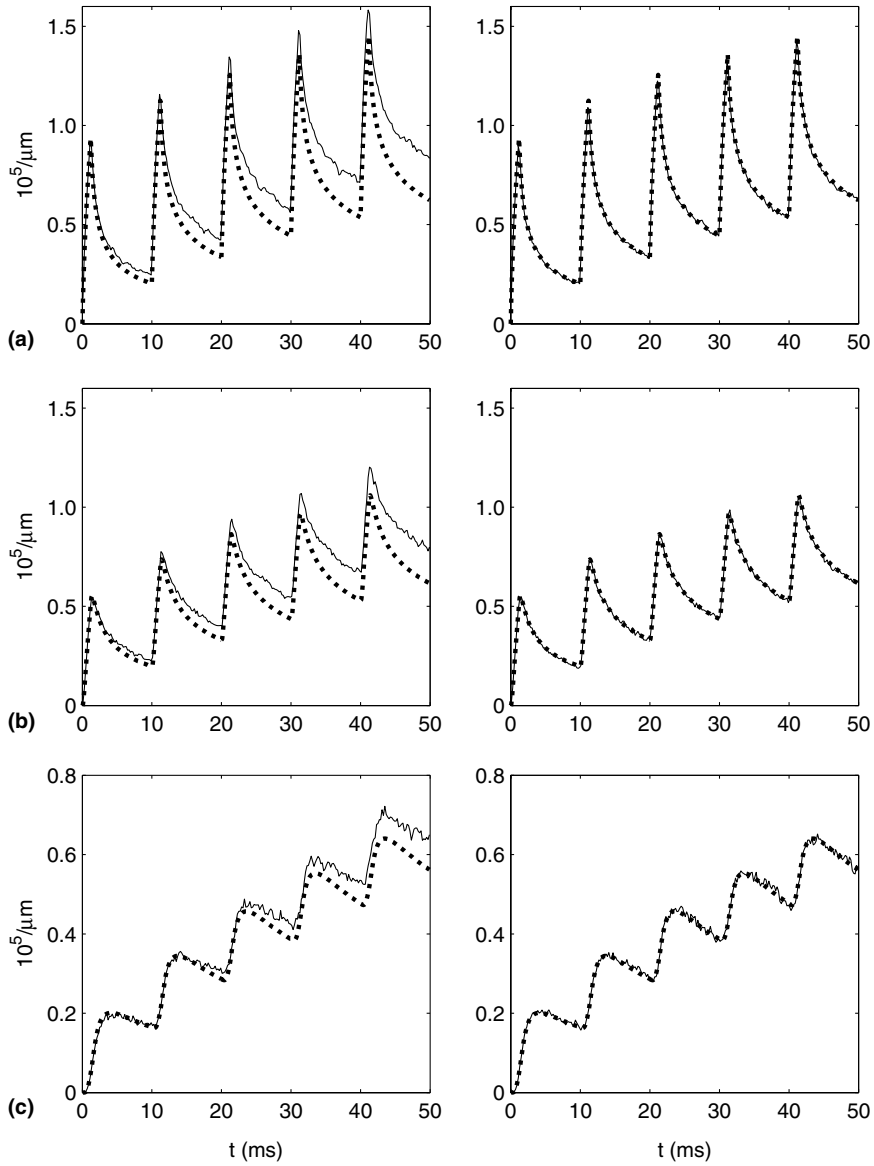

Fig. 4. Ca^{2+} diffusion under a linearly varying diffusion coefficient. The Ca^{2+} release protocol is the same as for Fig. 1; the diffusion coefficient is given by Eq. (17) with $D_0 = 4$ μm^2 s^{-1} and $\alpha = 1.4$ μm^{-1}. The left column shows the MC simulation results (solid line) when the uncorrected steplength Δx is used; the right column shows the corresponding results when the corrected steplength $\Delta x + \epsilon_1$ is used; in both cases $\Delta t = 0.15$ μs. In each panel, the broken line gives the deterministic result obtained by numerical solution of the diffusion equation.

where $D'(x_0) = \mathrm{d}D(x)/\mathrm{d}x$ evaluated at $x = x_0$, so provided the timestep is sufficiently small the linear theory can be used with D_0 replaced by $D(x_0)$ and α by $D'(x_0)/D(x_0)$; that is, the correction to the steplength is simply given by Eq. (21) with these replacements.

A practical way of proceeding is to write

$$D(x) = \widehat{D}s(x), \tag{23}$$

where $\widehat{D}$ is the homogeneous diffusion coefficient and $s(x)$ contains the spatial variation. Let $\widehat{\Delta x}$ be the Gaussian steplength appropriate for the constant diffusion coefficient $\widehat{D}$, as calculated using Eq. (6) or more conveniently Eq. (7), and let

$$\Delta x = \widehat{\Delta x}\sqrt{s(x_0)} \tag{24}$$

be the uncorrected steplength for position $x = x_0$. Then from Eq. (21) the corrected steplength is $\Delta x + \epsilon_1$, where

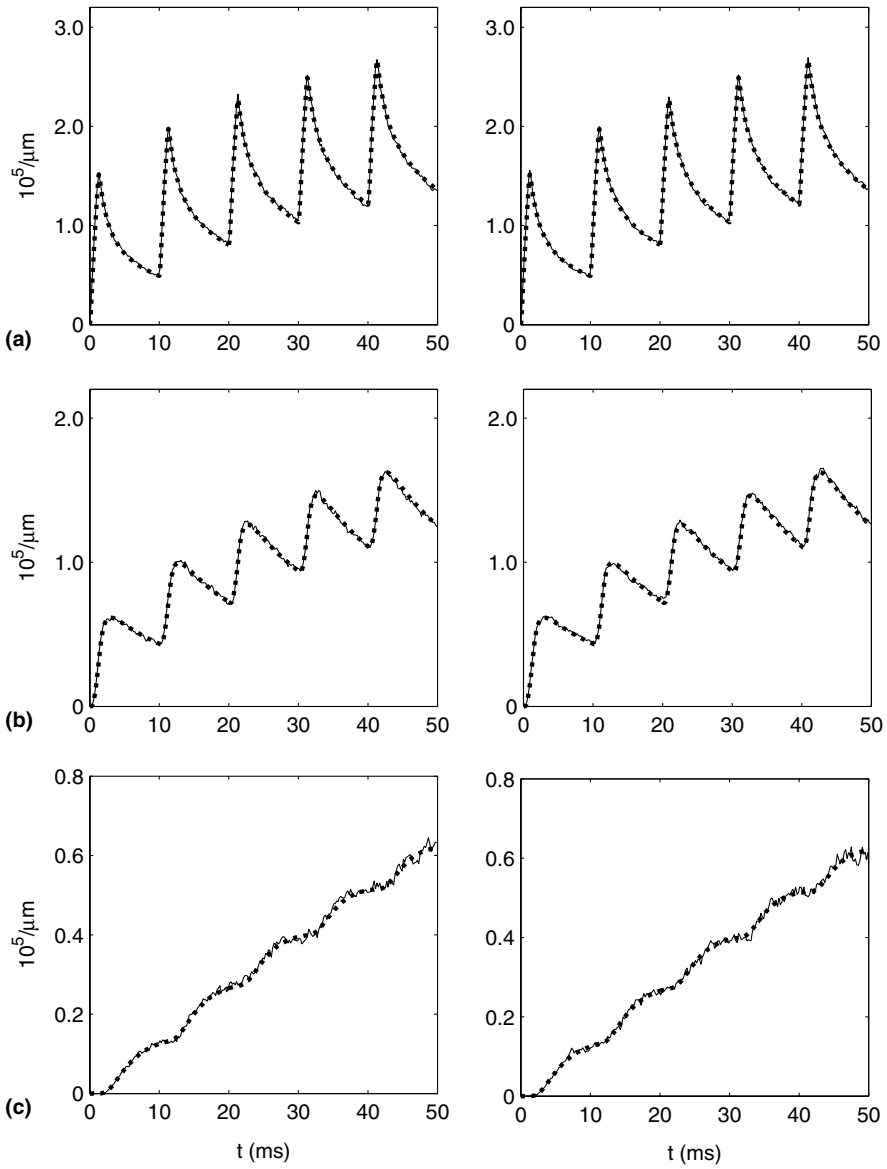

Fig. 5. Comparison of MC and deterministic results for the case of a variable diffusion coefficient, $D(x)$, as given by Eq. (9), when the MC stepsize is corrected using ϵ_1 as given by Eq. (21) (left column) and ϵ_2 as given by Eq. (A.16) (right column). The release protocol and parameter values are the same as those used in Fig. 2 and $\Delta t = 0.15$ μs.

$$\epsilon_1 = \frac{K(\widehat{\Delta x})s'(x_0)}{1 + M(\widehat{\Delta x})s'(x_0)/\sqrt{s(x_0)}}, \tag{25}$$

where $s'(x_0) = [\mathrm{d}s/\mathrm{d}x]_{x=x_0}$ and

$$K(\widehat{\Delta x}) = \frac{1}{2}\widehat{D}\Delta t + \frac{1}{4}(\widehat{\Delta x})^2, \tag{26}$$

$$M(\widehat{\Delta x}) = -\frac{1}{4}\widehat{\Delta x} + \frac{1}{8\widehat{D}\Delta t}(\widehat{\Delta x})^3. \tag{27}$$

The advantage of formulating the correction in this way is that once Δt has been chosen, a table of values of $K(\widehat{\Delta x})$ and $M(\widehat{\Delta x})$ can be constructed, using the fact that $\widehat{\Delta x}$ comes from a Gaussian distribution (compare the method given above in Section 2.1 for Δx in the homogeneous case), so the use of the correction ϵ_1 then only requires the evaluation of $s(x)$ and $s'(x)$ at each point.

As a practical demonstration of the use of the above formulas, we again treat the case presented by Matveev et al. [12], for simplicity still considering a one-dimensional version. In their case (see Eq. (9)),

$$s(x) = 1 - 0.8u(x), \tag{28}$$

where $u(x)$ is given by Eq. (10), so $\mathrm{d}s/\mathrm{d}x = 1.6Au(1-u)$ and the correction ϵ_1 as given by Eq. (25) is readily evaluated. The results are shown in Fig. 5 (left column) and should be compared with the results using the uncorrected steplength given in Fig. 2. It is seen that the MC average is now in good agreement with the deterministic calculation. Furthermore, use of the second-order correction ϵ_2 (see Appendix A) does not significantly improve the results (Fig. 5, right column).

The extension of the above to higher dimensions is straightforward, since each cartesian component can be stepped independently [2] and can be corrected independently using the gradient of the diffusion coefficient in the appropriate direction. Specifically, in three dimensions $D \equiv D(x,y,z)$ and

$$D(x_0 + \Delta x, y_0, z_0) = D(x_0, y_0, z_0)\left(1 + \frac{D_x(x_0, y_0, z_0)}{D(x_0, y_0, z_0)}\Delta x\right) + \mathcal{O}[(\Delta x)^2], \tag{29}$$

where $D_x \equiv \partial D/\partial x$, with similar expressions involving Δy and Δz. The uncorrected steplengths $\Delta x, \Delta y$ and Δz can now be calculated using equations analogous to Eq. (24), the corrections can be obtained from the analogues of Eq. (25), and hence the particle's position can be updated. We have checked that this procedure gives satisfactory results for a spherically symmetric case where release is from a single point and the diffusion coefficient is a function of the distance from this point.

3. Conclusion

Previous applications of the MC method to diffusion problems are to systems where the diffusion coefficient is either independent of position (homogeneous systems) or else the inhomogeneities are in the nature of impenetrable obstructions, in which case the boundary condition is that of reflection from the surface of the obstruction [11,15]. In the case of a spatially dependent diffusion coefficient, the "obvious" method is to replace the square root of the constant diffusion coefficient by the square root of the variable diffusion coefficient in the expression for the Gaussian steplength. A comparison of the distribution functions for the steplengths in the two cases would lead one to believe that this is likely to be a good approximation. Also, one would assume that reducing the timestep, and hence the average steplength, would reduce the error to any desired tolerance. However, a careful comparison with the deterministic

solution showed that this is not the case, and that there was a systematic error that did not reduce with the timestep. This systematic error can lead to erroneous conclusions; in the application discussed here the concentration of calcium ions at a specific location is the determining factor in the release of neurotransmitter and the postulated release mechanism is highly sensitive to the precise concentration. Also, it is often convenient to employ both deterministic and MC approaches to the same problem so agreement is vital if conclusions are to be consistent.

With hindsight, one can see why reducing the timestep does not reduce the error. Consider a situation where the diffusion coefficient increases from left to right. If the MC steplength were calculated using the local value of the diffusion coefficient without any correction, then each step to the left would be "too long" and each step to the right would be "too short". There is thus an inherent bias in the random walk and this persists regardless of the timestep; reducing this timestep does not help, as more steps are then required. This intuitive explanation is confirmed by Eq. (21), which shows that to leading order the required correction to the steplength is proportional to both the gradient of $D(\alpha)$ and the timestep (Δt).

We remark that an alternative way of simulating diffusion is to use a fixed steplength and then take each step randomly to the left or the right. As well as requiring more steps to give the same accuracy as the Gaussian-distribution method, this approach also suffers from the same type of systematic error for the case of a spatially dependent diffusion coefficient.

In this paper, we have presented a practical method of implementing the MC method when the diffusion coefficient depends on position. The method takes its starting point from the usual Gaussian steplength appropriate for a constant diffusion coefficient and a simple formula is given for the correction to this steplength arising from the spatial dependence. In general, this leading correction will be sufficient, but in extreme cases where the diffusion coefficient changes rapidly over a short distance it may be desirable to use a more accurate correction, and a formula for this has also been given. The calculations presented here all refer to a particular neurobiological context and have also been given in one dimension for simplicity, but the method of correcting the steplength is quite general and applicable to any problem involving non-homogeneous diffusion.

Appendix A

A.1. Solution of the diffusion equation for a linearly varying diffusion coefficient

We wish to solve the diffusion equation

$$\frac{\partial c}{\partial t} = \frac{\partial}{\partial x}\left(D\frac{\partial c}{\partial x}\right), \tag{A.1}$$

under the initial condition

$$c(x,0) = c_0\delta(x - x_0), \tag{A.2}$$

for the case where the diffusion coefficient $D(x)$ has a linear spatial dependence:

$$D(x) = D_0(1 + \alpha x), \tag{A.3}$$

where D_0 and α are constants, $D_0 > 0$.

A Laplace transform in t, together with the changes of variable $y = (1 + \alpha x)^{1/2}$ and $y_0 = (1 + \alpha x_0)^{1/2}$ leads to

$$\frac{\mathrm{d}^2 C}{\mathrm{d}y^2} + \frac{1}{y}\frac{\mathrm{d}C}{\mathrm{d}y} - \frac{4s}{D_0\alpha^2}C = -\frac{2c_0}{D_0|\alpha|y_0}\delta(y - y_0), \tag{A.4}$$

where

$$C \equiv C(y,s) \equiv \mathscr{L}_t\{c(x,t)\} = \int_0^\infty \mathrm{e}^{-st} c(x,t)\,\mathrm{d}t \tag{A.5}$$

is the Laplace transform of the concentration. Eq. (A.4) has solutions $I_0(\theta y)$ and $K_0(\theta y)$, where I_0 and K_0 are modified Bessel functions and $\theta = \sqrt{4s/D_0\alpha^2}$. Thus the general solution of Eq. (A.4) is

$$C(y,s) = \begin{cases} \mathscr{C}(s) I_0(\theta y) K_0(\theta y_0), & y < y_0, \\ \mathscr{C}(s) K_0(\theta y) I_0(\theta y_0), & y > y_0, \end{cases} \tag{A.6}$$

where $\mathscr{C}(s)$ can be determined from the "jump" condition

$$\left.\frac{\mathrm{d}C}{\mathrm{d}y}\right|_{y_0^+} - \left.\frac{\mathrm{d}C}{\mathrm{d}y}\right|_{y_0^-} = -\frac{2c_0}{D_0|\alpha|y_0}, \tag{A.7}$$

leading to $\mathscr{C}(s) = 2c_0/D_0|\alpha|$. The Laplace transform can then be inverted using [8, p. 495]

$$\mathscr{L}_s^{-1}\left\{ \begin{matrix} I_\nu(\sqrt{\frac{s}{\kappa}}x') K_\nu(\sqrt{\frac{s}{\kappa}}x), & x > x', \\ I_\nu(\sqrt{\frac{s}{\kappa}}x) K_\nu(\sqrt{\frac{s}{\kappa}}x'), & x < x', \end{matrix} \right\} = \frac{1}{2t}\mathrm{e}^{-(x^2+x'^2)/4\kappa t} I_\nu\left(\frac{xx'}{2\kappa t}\right), \tag{A.8}$$

giving

$$c(x,t) = \frac{c_0}{D_0|\alpha|t}\mathrm{e}^{-(y^2+y_0^2)/D_0\alpha^2 t} I_0\left(\frac{2yy_0}{D_0\alpha^2 t}\right). \tag{A.9}$$

A.2. Correction to the steplength

We wish to find a practical expression for the correction ϵ, as given by Eq. (16), for the case where the diffusion coefficient depends linearly on distance, Eq. (17). As explained in Section 2.4, this essentially involves expanding the distribution function $f_W(w)$, as given by Eq. (19), about the corresponding Gaussian distribution function for the case where w and t are small, with $w = \mathscr{O}(t^{1/2})$. Write Eq. (19) as

$$f_W(w) = \frac{|\alpha|}{\tau}\mathrm{e}^{-(2+v)/\tau} I_0\left(\frac{2\sqrt{1+v}}{\tau}\right), \tag{A.10}$$

where $v = \alpha w$ and $\tau = D_0\alpha^2 t$. Inserting the asymptotic expansion of the modified Bessel function [1, Section 9.7.1] gives

$$f_W(w) = \frac{|\alpha|}{\tau}\mathrm{e}^{\xi}\frac{1}{\sqrt{2\pi z}}\left[1 + \frac{1}{8z} + \mathscr{O}\left(\frac{1}{z^2}\right)\right], \tag{A.11}$$

where $z = 2\sqrt{1+v}/\tau$ and $\xi = -(2+v)/\tau + z$. The exponent has the expansion

$$\xi = \frac{1}{\tau}\left[-\frac{1}{4}v^2 + \frac{1}{8}v^3 - \frac{5}{64}v^4 + \mathscr{O}(v^5)\right] \tag{A.12}$$

and so

$$\mathrm{e}^{\xi} = \mathrm{e}^{-v^2/4\tau}\left[1 + \frac{1}{8}\frac{v^3}{\tau} - \frac{5}{64}\frac{v^4}{\tau} + \frac{1}{128}\frac{v^6}{\tau^2} + \mathscr{O}(v^3)\right]. \tag{A.13}$$

Also

$$\frac{|\alpha|}{\tau}\frac{1}{\sqrt{2\pi z}}\left[1+\frac{1}{8z}+\mathcal{O}\left(\frac{1}{z^2}\right)\right]=\frac{|\alpha|}{\sqrt{2\pi z}}\left[1-\frac{1}{4}v+\frac{5}{32}v^2+\frac{1}{16}\tau+\mathcal{O}(v^3)\right]. \tag{A.14}$$

Putting Eqs. (A.13) and (A.14) into Eq. (A.11) gives

$$f_W(w)=\frac{|\alpha|}{\sqrt{4\pi\tau}}\mathrm{e}^{-v^2/4\tau}\left[1+\left(-\frac{1}{4}v+\frac{1}{8}\frac{v^3}{\tau}\right)+\left(\frac{1}{16}\tau+\frac{5}{32}v^2-\frac{7}{64}\frac{v^4}{\tau}+\frac{1}{128}\frac{v^6}{\tau^2}\right)+\mathcal{O}(v^3)\right], \tag{A.15}$$

where terms of the same order have been bracketed. Putting this into Eq. (16) for ϵ and doing the integrals leads to the approximation

$$\epsilon\approx\epsilon_2=n_2/d_2, \tag{A.16}$$

where

$$n_2=\left(\frac{\alpha}{2}D_0\Delta t+\frac{\alpha}{4}(\Delta x)^2\right)+\left(-\frac{\alpha^2}{16}D_0\Delta t\Delta x-\frac{\alpha^2}{16}(\Delta x)^3+\frac{\alpha^2}{64}\frac{1}{D_0\Delta t}(\Delta x)^5\right) \tag{A.17}$$

and

$$d_2=1+\left(-\frac{\alpha}{4}\Delta x+\frac{\alpha}{8}\frac{1}{D_0\Delta t}(\Delta x)^3\right)+\left(\frac{\alpha^2}{16}D_0\Delta t+\frac{5\alpha^2}{32}(\Delta x)^2-\frac{7\alpha^2}{64}\frac{1}{D_0\Delta t}(\Delta x)^4+\frac{\alpha^2}{128}\frac{1}{(D_0\Delta t)^2}(\Delta x)^6\right). \tag{A.18}$$

If the higher order terms are omitted from Eq. (A.16) then we get the approximation ϵ_1 given by Eq. (21).

For the case where $D(x)$ is given by Eq. (23) a practical expression for the correction is (compare Eq. (25))

$$\epsilon_2=\frac{K(\widehat{\Delta x})s'+L(\widehat{\Delta x})s'^2/\sqrt{s}}{1+M(\widehat{\Delta x})s'/\sqrt{s}+N(\widehat{\Delta x})s'^2/s}, \tag{A.19}$$

where s and s' are to be evaluated at $x=x_0$, $K(\widehat{\Delta x})$ and $M(\widehat{\Delta x})$ are given by Eqs. (26) and (27), respectively, and

$$L(\widehat{\Delta x})=-\frac{1}{16}\widehat{D}\Delta t\widehat{\Delta x}-\frac{1}{16}(\widehat{\Delta x})^3+\frac{1}{64\widehat{D}\Delta t}(\widehat{\Delta x})^5, \tag{A.20}$$

$$N(\widehat{\Delta x})=\frac{1}{16}\widehat{D}\Delta t+\frac{5}{32}(\widehat{\Delta x})^2-\frac{7}{64\widehat{D}\Delta t}(\widehat{\Delta x})^4+\frac{1}{128(\widehat{D}\Delta t)^2}(\widehat{\Delta x})^6. \tag{A.21}$$

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