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Comparison of Continuous and Discrete Stochastic Ion Channel Models

Ciara Ellen Dangerfield, David Kay and Kevin Burrage

Abstract— **The stochastic behaviour of ion channels can be described by a discrete model or by an approximate continuous approach. While the discrete approach is exact, it is also less computationally efficient, and so the continuous model is often the method of choice since it allows for incorporation into a multiscale environment. However, in recent years the accuracy of the stochastic continuous approach for calculating statistics of certain quantities in the Hodgkin-Huxley model has come into question. In this paper, we show that by correct formulation of the continuous model, the first two moments in the number of open sodium and potassium channels in the Hodgkin-Huxley model, calculated under voltage clamp conditions using the continuous approach are in good agreement with those obtained from the discrete model.**

I. INTRODUCTION

Ion channels are specialised proteins that form a pore in the cell membrane and are a fundamental element in the generation of an action potential in excitable cells. They open and close at rates that depend on the membrane potential, V, and thus allow or restrict the movement of ions across the lipid bilayer. The movement of ion channels between these different states occurs at random. This stochastic behaviour is thought to be important to the electrical activity of neurons [1], and cardiac myocytes [2].

In recent years a number of models and computational algorithms have been developed that aim to accurately and efficiently capture stochastic ion channel kinetics [3], [4], [5], [6]. These models use either a discrete exact method or an approximate continuous approach. Typically the channel is assumed to reside in one of k discrete states at time t with the probability of transition between states dependent on its current position, [7]. This construction of channel behaviour will be referred to as state formulation. Exact methods model the channel as a discrete-state continuous-time Markov process. Various algorithms have been developed to simulate the dynamics of this process, [3], [5], and can be used to obtain the time evolution in the number of channels in each state.

When the total number of channels, N_{tot}, is relatively large this discrete model can be approximated by a continuous-state continuous-time Markov chain. The dynamics of this process can be described by an Itô type stochastic differential equation (SDE), which takes the form of a Langevin equation, [8]. This approach assumes that the deterministic model is perturbed by a Gaussian noise with magnitude proportional to $1/\sqrt{N_{tot}}$. Individual trajectories can be obtained by solving the SDE using one of the many numerical methods that have been developed, [9]. The solution provides the time evolution in the proportion of channels in each state, rather than the discrete number. Although this approach is not exact, for relatively large numbers of channels this approximation captures the general behaviour of the discrete system quite well. The main advantage of the continuous approach over exact methods is that they are more computationally efficient and so allow for incorporation into multiscale models.

The Fox and Lu algorithm, given in [4], makes a further approximation to improve the efficiency of the SDE model. Ion channels are often assumed to consist of a series of independent gates that can be either open or closed. The channel is open only when all gating particles are in the open position. This construction of channel behaviour will be referred to as gating formulation. The dynamics of each gating variable can be described by an ordinary differential equation (ODE) and the proportion of open channels is estimated to be the product of the proportion of open gates. In [4] the SDE describing the dynamics of the state formulation of the channel is approximated by the stochastic version of the ODEs that describe the gating variables. This approach has been widely used in the literature, [10], [11], [2], as it is around seven times faster than the most efficient discrete algorithm. However, a number of recent studies, [12], [13], [14], have found that the approach produces quite different action potential statistics compared to exact methods. In particular, in [13] it was shown that under voltage clamp conditions in the Hodgkin-Huxley model, the second moment in the number of open channels differs significantly between the Fox and Lu algorithm and an exact approach.

In [4] and [15] a SDE describing the state formulation of ion channel dynamics was derived from the discrete-state Markov process. The form of the noise term involved the square root of a matrix, reducing the computational efficiency of the model. This was the motivation given for the further approximation that is made in [4].

We show that the square root of the matrix in [4] and [15] can be calculated directly, rather than numerically, as the product of a diagonal matrix and a matrix of 0's and 1's, [16]. This form of the channel SDE is thus more computationally efficient as it does not require numerical calculation of a matrix square root. We note that the square root of this matrix is not unique and other forms exist, [8], although they are not as efficient as the form presented here. This paper will focus on the stochastic behaviour of the sodium and potassium channels in the Hodgkin-Huxley model. Using voltage clamp protocol we show that, unlike the Fox and Lu algorithm, the

C.E. Dangerfield, D. Kay and K. Burrage are with the Computing Laboratory, University of Oxford, Oxford, UK

K. Burrage is also with the Department of Mathematics, Queensland University of Technology, Brisbane, Australia

Email: ciara.dangerfield@dtc.ox.ac.uk

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second moment in the number of open channels for the SDE describing the state formulation of the channel is consistent with that for a discrete method. Therefore by using the correct construction of the continuous model, voltage clamp statistics between the discrete and continuous approaches are similar. The algorithm used to simulate the dynamics of the discrete process is given in [5], since this is the most efficient of the exact schemes, [12].

In the methods section the dynamics of the sodium and potassium channels in the Hodgkin-Huxley model are given. We also describe in more detail the discrete method, the SDE for the state formulation of the channel dynamics and the Fox and Lu algorithm that are used. Finally in this section, a method for exactly obtaining the mean and variance of a continuous stochastic process described by a SDE is given. In the results section we show that the second moment in the number of open channels for the discrete process and the state formulation SDE are similar, while the second moment of the Fox and Lu algorithm is significantly different. We show this issue does not improve as the number of channels increases. Finally we conclude with some remarks on the shortcomings of current numerical algorithms in accurately solving the SDEs that describe channel behaviour.

II. METHODS

A. Stochastic Models of Ion Channel Dynamics

The Hodgkin-Huxley model, [17], supposes that the sodium channel consists of three identical activation gates, m, and one inactivation gate, h, while the potassium channel has four identical gates, n. Each gate, x, can be either open or closed at time t and transitions from open to closed and vice versa at rates $a_x(V)$, $b_x(V)$ respectively that depend on the membrane potential V. Letting each possible configuration of open and closed gates represent a different state of the channel, the Markov kinetics of the sodium and potassium channels are given by the following state diagrams respectively.

$$\begin{array}{ccccccc} m_0h_0 & \underset{b_m}{\overset{3a_m}{\rightleftarrows}} & m_1h_0 & \underset{2b_m}{\overset{2a_m}{\rightleftarrows}} & m_2h_0 & \underset{3b_m}{\overset{a_m}{\rightleftarrows}} & m_3h_0 \\ b_h\uparrow\downarrow a_h & & b_h\uparrow\downarrow a_h & & b_h\uparrow\downarrow a_h & & b_h\uparrow\downarrow a_h \\ m_0h_1 & \underset{b_m}{\overset{3a_m}{\rightleftarrows}} & m_1h_1 & \underset{2b_m}{\overset{2a_m}{\rightleftarrows}} & m_2h_1 & \underset{3b_m}{\overset{a_m}{\rightleftarrows}} & m_3h_1 \end{array}$$

$$n_0 \underset{b_n}{\overset{4a_n}{\rightleftarrows}} n_1 \underset{2b_n}{\overset{3a_n}{\rightleftarrows}} n_2 \underset{3b_n}{\overset{2a_n}{\rightleftarrows}} n_3 \underset{4b_n}{\overset{a_n}{\rightleftarrows}} n_4$$

Let $N_i(t)$ denote the number of channels in state i at time t. The chance that a channel shifts from i to j at time t is then $\gamma_{ij}(t) = r_{ij}N_i(t)$, where r_{ij} is the rate at which transition from state i to state j occurs, given in the diagrams above. Note that the following conservation law holds, $\Sigma_{i=1}^{d} N_i(t) = N_{tot}$, where N_{tot} is the total number of sodium or potassium channels in the cell and d is the number of transitions the channel can undergo. Since transitions between states are reversible d is always even. The channel is assumed to be in the open state only when all gating variables are open and so the number of open sodium and potassium channels are given by $N_{m_3h_1}(t)$ and $N_{n_4}(t)$ respectively.

Individual trajectories of these processes can be generated by the Stochastic Simulation Algorithm, SSA, [18], as in [5]. This is an exact method that tracks the number of channels in each state. Other discrete numerical schemes track the state of every channel over time, [6], [3], but are less efficient approaches [12].

The SSA calculates the waiting time τ until the next transition and updates the number of channels in each state based on the most likely transition to have occurred. The waiting time is sampled from an exponential distribution with rate $\lambda(t) = \sum_{i,j} \gamma_{ij}(t)$. The most likely transition to occur is then determined based on sampling a uniform random number on $[0, 1]$ from d subintervals of length $\gamma_{ij}(t)/\lambda(t)$. Finally the state of the system is updated according to which transition has taken place.

As N_{tot} increases, the discrete model for the sodium and potassium channels can be closely approximated by a continuous-state Markov process. Let $\boldsymbol{y}(t)$ be a vector whose entries denote the proportion (rather than number) of channels in each state at time t. Column number e of the matrix υ denotes the change to the number of channels in each state as a result of transition e. The chance of transition e occurring ($r_{ij}y_i(t)$ for some i j) is the (e, e)'th entry of the diagonal matrix $D(\boldsymbol{y}(t))$. The Langevin equation for a channel that can reside in k states and undergo d transitions is then given by, [16],

$$d\boldsymbol{y}(t) = \upsilon D(\boldsymbol{y}(t))dt + \tfrac{1}{\sqrt{N_{tot}}}\Sigma_{p=1}^{d/2} b^p(\boldsymbol{y}(t))dW_p, \qquad (1)$$

where N_{tot} is the number of channels and $b^p(\boldsymbol{y}(t))$ are the columns of the matrix, $B(\boldsymbol{y}(t))$, a k by $d/2$ matrix that satisfies $BB^T = \upsilon D(\boldsymbol{y}(t))\upsilon^T$. The dW_j are Wiener increments which are sampled from a normal distribution with mean 0 and variance h. Note the first term in the above equation represents the standard deterministic model for the state formulation of the channel dynamics. For this continuous model, the number of channels in the open state at time t is simply $N_{tot}y_O(t)$ where O is the open state.

Since channel transitions are reversible, in [16] they show that the matrix B can be constructed in a manner that gives a much simpler form of the noise terms than is presented in [4] and [15]. The matrix B can be decomposed into two matrices, $B = ES$, where E is a $k \times d/2$ matrix and S is a $d/2 \times d/2$ diagonal matrix. E has two non-zero entries in each column that are 1 and -1 and the diagonal entries of S are of the form $\sqrt{r_{ij}y_i(t) + r_{ji}y_j(t)}$ for some i and j. Therefore the vector $b^p(\boldsymbol{y}(t))$ for $1 \le p \le d/2$ has two non-zero entries of the form

$$\pm\sqrt{r_{ij}y_i(t) + r_{ji}y_j(t)},$$

for some i and j. For example, the E matrix and the diagonal entries of the S matrix for the potassium channel are respectively,

$$\begin{pmatrix} 1 & 0 & 0 & 0 \\ -1 & 1 & 0 & 0 \\ 0 & -1 & 1 & 0 \\ 0 & 0 & -1 & 1 \\ 0 & 0 & 0 & -1 \end{pmatrix}, \begin{pmatrix} \sqrt{a_n y_{n_3} + 4b_n y_{n_4}} \\ \sqrt{2a_n y_{n_2} + 3b_n y_{n_3}} \\ \sqrt{3a_n y_{n_1} + 2b_n y_{n_2}} \\ \sqrt{4a_n y_{n_0} + b_n y_{n_1}} \end{pmatrix}. \qquad (2)$$

The form of the SDE for the state formulation of the channel dynamics given by (1) is around seven times faster at each time step than the SDE derived in [4] and [15] since it does not involve the square root of a matrix.

Instead of modelling the proportion of channels in each state by the SDE (1), the Fox and Lu algorithm described in [4] approximates the fraction of open gating particles of type x by the following SDE

$$\frac{dx(t)}{dt} = (a_x - (a_x + b_x)x(t))dt + \frac{1}{\sqrt{N_{tot}}}\sqrt{a_x + (b_x - a_x)x(t)}dW, \quad (3)$$

where N_{tot} is the total number of sodium or potassium channels. The proportion of open channels is then estimated to be the product of the stochastic gating variables. So the proportion of open sodium and potassium channels at time t are given by $m(t)^3h(t)$ and $n(t)^4$ respectively, where the variables $m(t)$, $h(t)$ and $n(t)$ are calculated using (3).

B. First two moments of the number of open channels

The first two moments in the number of open channels for the discrete approach is estimated using 1000 simulations of the SSA. However, for a system of SDEs the first two moments can be calculated exactly, as in [19] and that is the approach taken in this paper. To the best of our knowledge, an analytic calculation of the first two moments of (1) and (3), in the manner described below, has not previously been presented.

Taking the expectation in (1) and (3) and noting that the expectation of dW is 0, we obtain the following ODEs describing the mean of the processes $\boldsymbol{y}$ and x,

$$\frac{dE(\boldsymbol{y})}{dt} = \upsilon D(E[\boldsymbol{y}(t)]), \quad (4)$$

$$\frac{dE[x]}{dt} = (a_x - (a_x + b_x)E[x(t)]). \quad (5)$$

since $D(\boldsymbol{y}(t))$ is linear. The mean proportion of open channels calculated using (1) is thus given by $E[y_O(t)]$, where O represents the open state in the vector $E[\boldsymbol{y}(t)]$ which is the solution to (4). Alternatively the mean proportion of open channels calculated using the Fox and Lu algorithm, (3), for the sodium and potassium channels are $(E[m])^3E[h]$ and $(E[n])^4$ respectively, where $E[x]$, $x = m, h, n$, is the solution to (5).

An ODE describing the evolution of the second moment in the proportion of open channels for the process described by (1) can be obtained by applying Itô's Lemma [9] to the function $f(\boldsymbol{y}) = y_O^2$ and taking expectations. Itô's Lemma is the stochastic analogue of the chain rule and was used in [19] to obtain the mean and variance of SDEs that model biochemical reaction networks.

Similarly, applying Itô's Lemma to the function $g(x) = x^2$, the second moment of the stochastic gating variables, given by (3) can be derived. The second moment in the proportion of open sodium and potassium channels for the Fox and Lu algorithm is thus estimated to be $(E[m^2])^3E[h^2]$, and $(E[n^2])^4$ respectively.

III. RESULTS

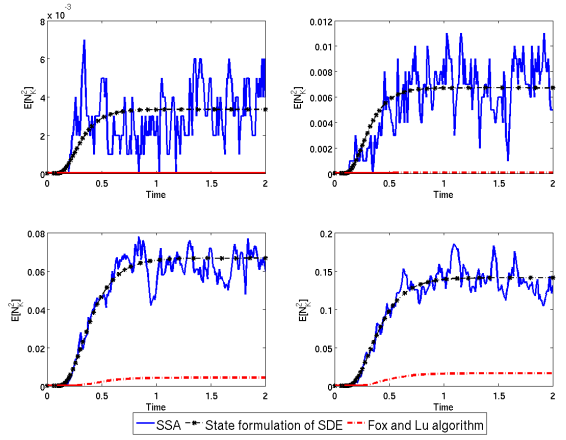

Fig. 1. Time evolution in the second moment of the number of open channels for the three stochastic simulation methods. The number of channels is 333 (left) or 666 (right). The voltage step is $16mV$ (top) or $24mV$ (bottom).

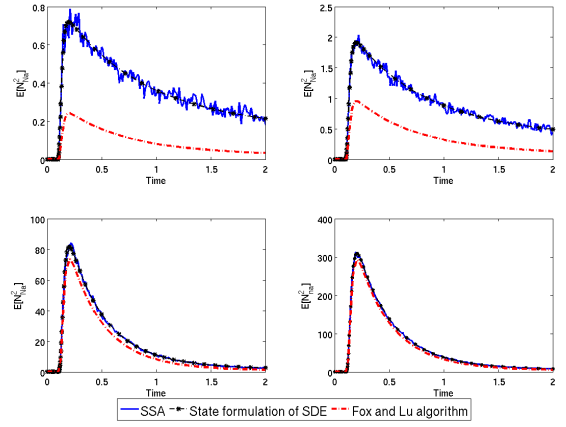

Fig. 2. Same as (1), but for the sodium channel, with the number of channels set to 1000 (left) or 2000 (right). In the bottom two plots the results for the three methods virtually lie on top of one another.

The open channel statistics were calculated for voltage clamp experiments using the same protocol as in [13]. The initial holding potential was set to the resting potential ($V = 0$) and after $0.1ms$ it was stepped up to a value of V_c. Two different voltage step sizes were simulated, $V_c = 24mV$ and $V_c = 16mV$. The transition rates for each gating variable (a_x, b_x for $x = m, h, n$) vary with respect to the transmembrane potential, V, according to the functions (18) to (23) in [13]. The first two moments of the discrete stochastic model, i.e. the SSA formulation, are calculated over 1000 repetitions for each voltage step, while for the continuous models, (1) and (3), they are calculated in the manner described at the end of the previous section.

We find that the mean number of open sodium and potassium channels for (1) and the Fox and Lu algorithm are both in good agreement with that obtained using multiple simulations of the SSA, as reported in [13]. We therefore

omit these results (see [13] Fig. 2). For each voltage step the total number of sodium channels is set to 1000 or 2000 and the total number of potassium channels is 333 or 666

From Fig. 1 and Fig. 2 it is clear that the second moment in the number of open channels for the state formulation SDE, (1), is in good agreement with the discrete model, while the Fox and Lu algorithm differs significantly from both. In particular we note that this issue with the Fox and Lu algorithm does not noticeably improve as the total number of channels increases.

IV. CONCLUSIONS AND FUTURE WORKS

In this paper we showed that the second moments in the number of open sodium and potassium channels in the Hodgkin-Huxley model calculated using the Fox and Lu algorithm significantly differs from the state formulation SDE, (1), and the discrete model. Therefore, the discrepancies between continuous and discrete models, as reported in [13], are not due to the continuous stochastic approximation but are a result of the further simplification made in [4], namely that the stochastic behaviour of the state formulation of the channel can be approximated by the stochastic equations for the gating variables. This simplification was made since the state formulation SDE derived in [4] is computationally expensive due to the matrix square root. However, we have shown here that due to the special structure of the system, this SDE can take a much simpler form than was given in [4] and [15]. The main increase in computational cost of the SDE we give, (1), as compared with the Fox and Lu algorithm is that at each time step more Wiener increments need to be sampled. However, this increase is not significant since all the Wiener increments can be generated at the start of the simulation. Thus we have provided a continuous stochastic method with computational speed comparable to that of the Fox and Lu algorithm, but that preserves the first two moments of the exact discrete model.

An extension would be to compare the firing statistics obtained from these three methods to see if the continuous model we have given is still in good agreement with the discrete algorithm. Such statistics must be calculated over multiple simulations of the continuous model, rather than analytically as we were able to do here. While there are many efficient numerical methods for solving SDEs [9], such schemes do not guarantee that the proportion of channels in each state will remain positive and in certain cases solutions can become imaginary. For the simplest model where the channel is either open or closed, the numerical scheme can be altered to force solutions to remain positive by continualy resampling the Wiener increment, as is done in [4]. However, such alternations have been shown to bias the solution, [20], and so would not provide a fair comparison between the discrete and continuous models. Furthmore, such an alteration is not viable for more complex models such as those given here. In [15] they alter the state formulation SDE by replacing the variables in the noise term by their equilibrium value, ensuring solutions remain real although not preserving positivity. It is possible that such an alteration could bias the SDE solution and so using such a method would not provide a fair comparison between the discrete and continuous models. We point out that this constraint is due to issues with accurate numerical algorithms for simulating the dynamics of the SDEs rather than with the continuous model itself. Therefore for fair detailed statistical comparisons between the continuous and discrete models, numerical algorithms that are able to preserve the boundaries of solutions to SDEs must be developed, which we leave to future study.

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