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A boundary preserving numerical algorithm for the Wright-Fisher model with mutation

C.E. Dangerfield · D. Kay · S. MacNamara · K. Burrage

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Abstract The Wright-Fisher model is an Itô stochastic differential equation that was originally introduced to model genetic drift within finite populations and has recently been used as an approximation to ion channel dynamics within cardiac and neuronal cells. While analytic solutions to this equation remain within the interval $[0, 1]$, current numerical methods are unable to preserve such boundaries in the approximation. We present a new numerical method that guarantees approximations to a form of Wright-Fisher model, which includes mutation, remain within $[0, 1]$ for all time with probability one. Strong convergence of the method is proved and numerical experiments suggest that this new scheme converges with strong order $1/2$. Extending this method to a multidimensional case, numerical tests suggest that the algorithm still converges strongly with order $1/2$. Finally, numerical solutions obtained using this new method are compared to those obtained using the Euler-Maruyama method where the Wiener increment is resampled to ensure solutions remain within $[0, 1]$.

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C.E. Dangerfield (✉) · D. Kay · K. Burrage
Oxford University Department of Computer Science, Wolfson Building, Parks Road, Oxford, OX1 3QD, UK
e-mail: ciara.dangerfield@cs.ox.ac.uk

D. Kay
e-mail: dkay@cs.ox.ac.uk

S. MacNamara
Mathematical Institute, 24-29 St Giles', Oxford, OX1 3LB, UK
e-mail: Shev.Macnamara@maths.ox.ac.uk

K. Burrage
Department of Mathematics, Queensland University of Technology, Brisbane, Queensland, Australia
e-mail: kevin.burrage@cs.ox.ac.uk

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1 Introduction

The Wright-Fisher model describes the stochastic fluctuations in gene frequency among a finite population of reproducing individuals, [5]. When the population size is large, the dynamics are given by an Itô stochastic differential equation, SDE, [20]. This equation is of importance in the study of population dynamics as it can be used to calculate quantities such as the expected time until a single gene remains. In a different setting this equation can also be used to approximate the Langevin SDE that describes the random behaviour of ion channels within cardiac and neuronal cells.

The Wright-Fisher SDE models the change in the proportion of a specific type of gene within a population over time and analytic solutions can be shown to remain within the interval $[0, 1]$, [20]. When mutation is included into the model then under certain parameter regimes, solutions will not hit the boundary of this interval in finite time. The issue is that commonly used numerical techniques, such as the Euler-Maruyama and Milstein methods, [21], are unable to preserve the boundaries to the solution of this SDE. This is because as the approximation becomes close to the boundary, at the next time step the Wiener increment can be large enough to force the solution out of the interval $[0, 1]$. There are two commonly used alterations that are made in the numerical algorithm to force approximations to remain within the desired region. If the solution goes out of the interval then the Wiener increment is resampled until the approximation at that time step remains in $[0, 1]$, as is done in [7, 28]. Alternatively, if the approximation becomes negative or is greater than 1 then the solution at that time step is set to 0 or 1, respectively. The problem is that such alterations can introduce bias into the numerical solution, [22].

In recent years a number of numerical schemes that aim to preserve the boundaries of solutions to SDEs have been developed. Most techniques have focused on algorithms that ensure positive numerical solutions to mean-reverting square root processes in financial models. The Balanced Implicit Method (BIM) incorporates implicitness into the Euler-Maruyama scheme, [24], and was shown in [29] to preserve the boundaries of a mean reverting process with cubic diffusion and a model of diffusion of innovation in marketing sciences. In [18] the Balanced Milstein Method (BMM), an extension to the BIM, was developed and was shown to preserve positivity for a class of SDEs whose diffusion coefficients satisfied a number of conditions. In recent years a number of splitting step methods have been constructed to preserve the positivity of solutions to models in finance. A scheme that splits one dimensional SDEs into a SDE whose analytic solution is known and an ordinary differential equation (ODE) was developed in [25] and shown to preserve positivity for the Cox Ingersoll Ross (CIR) model, [3], and constant elasticity volatility models. However this

algorithm is difficult to implement for multidimensional systems since few analytical solutions of higher dimensional SDEs are known. Other splitting methods have utilised techniques to solve ODEs such as the Strang splitting method, [11, 26], and Jacobi splitting, [12], in order to preserve the positivity of solutions to mean reverting square root processes under certain parameter regimes. The main issue with current boundary preserving algorithms is that many methods are model dependent [25], or they only work under certain parameter regimes [11, 12, 17, 26] and so they do not necessarily generalise to Wright-Fisher models.

In this paper, we propose a novel numerical method for the solution of the Wright-Fisher model, for the specific case where mutation is included, that ensures approximations remain within the interval [0, 1] for all time. This method combines two existing schemes, the Balanced Implicit Method (BIM) [24] and the Moro and Schurz split step method [25], using a special property of the BIM for the Wright-Fisher model to ensure that numerical solutions remain within [0, 1]. This scheme is shown to converge in the strong sense and numerical tests suggest that the order of convergence is $1/2$ for both scalar and multidimensional forms.

We begin with a brief introduction to the Wright-Fisher model and discuss its use in modelling ion channel dynamics within cardiac and neuronal cells. In Sect. 3 we formalise what it means for a numerical method to preserve the boundaries of a SDE. We introduce the numerical scheme and show that it is boundary preserving for the Wright-Fisher model with mutation in Sect. 4 and in Sect. 5 the strong convergence of the method is proved. Numerical experiments that suggest the scheme converges with strong order $1/2$ for the one-dimensional and multidimensional Wright-Fisher models with mutation are presented in Sect. 6. We apply the new method to one of the gating variables for the sodium ion channel in the Hodgkin-Huxley model [16], an electrophysiology model of a neuronal cell, where the membrane potential is fixed in Sect. 7. The solution is compared to that obtained using the Euler-Maruyama method where the Wiener increment is resampled to ensure solutions remain within [0, 1]. Finally the new method is used to solve the ion channel equations in the full Hodgkin-Huxley model where the membrane potential varies over time.

2 Wright-Fisher model

The Wright-Fisher model is a simple model describing the stochastic evolution of a population and was introduced in the 1930s independently in [6, 30]. The most basic version of the model assumes that there are two types of alleles, r_1 and r_2 for a gene in a population whose total size, N, remains constant from one generation to the next. Since the total number of alleles in the population remains constant, i.e. $r_1 + r_2 = N$, it is sufficient to consider the number, $Y(\tau)$ of a single allele r_1 at generation τ. The gene pool of the kth generation is sampled to give the genetic structure of the $(k+1)$th generation.

This model can be extended to include the possibility of alleles mutating from one generation to the next. Let us assume that a r_2 allele mutates to a r_1 allele over one generation with probability A and a r_1 mutates to a r_2 with probability B. The transition probabilities that the system moves from state i to state j over

one generation, P_{ij}, follow a binomial distribution with the probability of success $p_i = \frac{i(1-A)+B(N-i)}{N}$ and the number of trials equal to the population size N,

$$P_{ij} = \binom{N}{j} p_i^j (1-p_i)^{N-j}. \tag{2.1}$$

When the population size is large, the Wright-Fisher model with mutation can be approximated by a continuous state continuous time process, $Y(t)$, which represents the proportion of alleles of type r_1 in the population and is described by the following SDE, [20]

$$dY = (A - (A+B)Y)dt + \sqrt{Y(1-Y)}dW, \tag{2.2}$$

where dW is a Wiener increment. A Wiener process, $W(t)$, is a stochastic process whose increment on the interval $[t, t+\Delta_t]$, defined by $dW(t) = W(t+\Delta_t) - W(t)$, satisfies the properties $\mathbb{E}(dW(t)) = 0$, $\mathbb{E}(dW(t) - \mathbb{E}(dW(t)))^2 = \Delta_t$ and Wiener increments on non-overlapping intervals are independent. From here on we refer to the Wright-Fisher SDE or model as that which includes mutation between alleles, (2.2). The analytic solution to (2.2) can be shown to remain within [0, 1] for all time, [20]. In [9, 10] the Wright-Fisher SDE given by (2.2) has been extended to the multidimensional case that describes the dynamics of $d+1$ different alleles that can undergo m reversible mutations.

A different setting in which a form of the Wright-Fisher SDE has been used is as an approximation to the dynamics of ion channels within cardiac and neuronal cells. Ion channels are specialised proteins that lie in the membrane of excitable cells and are assumed to reside in one of m discrete states with transition rates between states depending on the membrane potential, V. The ion channel transitions from one state to another at random and the evolution of the proportion of channels in each state can be described by an Itô SDE taking the special form of a Langevin equation, [8, 23]. The issue is that for the simplest system, where the ion channel is assumed to occupy one of two positions, analytic solutions to the Langevin equation can leave the interval [0, 1], questioning the biological relevance of this model. In [4] we suggested using a form of the Wright-Fisher model described by the Itô SDE

$$dY = (\tilde{A} - (\tilde{A} + \tilde{B})Y)dt + \tilde{C}\sqrt{Y(1-Y)}dW \tag{2.3}$$

as an approximation to the stochastic dynamics of the simple ion channel model. If a and b are the transition rates between closed and open and open and closed states respectively then setting the parameters in (2.3) to be

$$\tilde{A} = a, \qquad \tilde{B} = b, \qquad \tilde{C} = \sqrt{\frac{2(a+b)}{N-1}}, \tag{2.4}$$

where N is the total number of ion channels within a cell, ensures the mean of (2.3) is identical to that of the Langevin equation and the difference in the variance of these two equations is of the order $1/N$. Therefore (2.3) and (2.4) provide an alternative model for the stochastic behaviour of ion channels with biologically realistic solutions, whilst still providing a good approximation to the mean and variance of the Langevin equation.

Using (2.3) to model ion channel dynamics adds a level of complexity to the numerical methods employed to solve this equation since the parameters are no longer constant but are functions of the membrane potential V and so will vary over time. Providing the discretisation time step used in the simulation is small, the voltage can be assumed to remain *frozen* over each time step and so the rates at which the channel transitions from one state to another are constant. Hence, over each time step (2.3) can be solved assuming that the parameters $\tilde{A}$, $\tilde{B}$, and $\tilde{C}$ are constant. The main complication of voltage dependent transition rates is that the numerical scheme used to solve (2.3) must preserve the boundaries of 0 and 1 for all physiologically realistic parameter regimes. Otherwise this limits the ability for incorporation into an electrophysiological model where the membrane potential varies over time, such as the Hodgkin-Huxley model [16].

Throughout this paper we assume that the parameters $\tilde{A}$, $\tilde{B}$, and $\tilde{C}$ are strictly positive, $\tilde{A}$, $\tilde{B}$, $\tilde{C} > 0$, as is the case for electrophysiology models of cardiac and neuronal cells, [16, 27]. In the next three sections we also assume that the parameters in (2.3) are constant.

3 The lifetime of a numerical method

The concept of a boundary preserving numerical scheme was formalised by Schurz in [29]. He introduced the notion of an algorithm having *eternal lifetime* which is defined as follows.

Definition 3.1 [29] Let y_n be computed from a stochastic numerical scheme that approximates the solution to the Wright-Fisher model, (2.3), where y_n is the approximation at time t_n. The numerical scheme y_n is said to possess eternal lifetime if

$$P\left(y_n \in [0,1] | y_0 \in [0,1]\right) = 1, \quad \text{for all } n > 0. \tag{3.1}$$

If (3.1) does not hold then the numerical scheme is said to have finite lifetime and so the approximation can leave the interval $[0,\ 1]$ with positive probability. A weaker notion of a boundary preserving numerical scheme is that of ϵ-lifetime.

Definition 3.2 [29] Let y_n be computed from a stochastic numerical scheme that approximates the solution to the Wright-Fisher model, (2.3), where y_n is the approximation at time t_n. The numerical scheme y_n is said to possess ϵ-lifetime if

$$P\left(y_n \in [0,1] | y_{n-1} \in [\epsilon, 1-\epsilon]\right) = 1, \quad \text{for some } \epsilon > 0. \tag{3.2}$$

This property provides a one step assurance that the approximation to (2.3) will lie within the correct region. However, since y_n can lie in the region $[0, \epsilon) \cup (1-\epsilon, 1]$ with positive probability, at time t_{n+1} the numerical solution is not guaranteed to remain within $[0, 1]$ and so this property does not ensure the discretisation scheme is boundary preserving for all time.

4 A boundary preserving numerical scheme for the Wright-Fisher model

The Balanced Implicit Split Step (BISS) method is a combination of the Balanced Implicit Method (BIM), first introduced in [24], and the split step method developed in [25]. In what follows we shall consider the numerical approximation to the Wright-Fisher model on a fixed time interval $[0, T]$ with discretisation $t_0 = 0, \ldots, t_M = T$ where $t_{n+1} - t_n = \Delta_{t_n}$ for $0 \leq n \leq M-1$. For simplicity we assume a fixed time step $\Delta_{t_n} = \Delta_t$ throughout. We begin with a brief description of the two methods on which the BISS scheme is based.

4.1 BIM method

The Balanced Implicit Method (BIM) was introduced in [24] as a method for solving stiff stochastic systems. Unlike drift implicit methods, the scheme introduced implicitness into the diffusion term as well as the drift term through a system of freely chosen control functions, $d^j(X)$. In [1] the optimal choice for the control functions with respect to the local truncation error in strong convergence are given and shown to improve the accuracy of the scheme.

The BIM for the Wright-Fisher model, (2.3), can be described by the one-step discretisation scheme (where we have removed the tildes from the parameters)

$$y^B_{n+1} = y^B_n + (A - (A+B)y^B_n)\Delta_t + C\sqrt{y^B_n(1-y^B_n)}\Delta W_n + D(y^B_n)(y^B_n - y^B_{n+1}), \tag{4.1}$$

where Δ_t is the length of the time discretisation interval and ΔW_n is a Wiener increment. In the update formula above, $D(y^B_n)$ is the system of control functions and takes the form,

$$D(y^B_n) = d^0(y^B_n)\Delta_t + d^1(y^B_n)|\Delta W_n|. \tag{4.2}$$

Although the BIM scheme was originally introduced as a method for solving stiff stochastic systems, in [29] Schurz showed that by careful choice of the control functions the BIM scheme possesses ϵ-lifetime for the Wright-Fisher model with no drift, i.e. the case $A, B = 0$. The control functions that ensure such a property are

$$d^1(y) = \begin{cases} C\sqrt{\frac{1-\epsilon}{\epsilon}} & \text{if } y < \epsilon, \\ C\sqrt{\frac{1-y}{y}} & \text{if } \epsilon \leq y < 1/2, \\ C\sqrt{\frac{y}{1-y}} & \text{if } 1/2 \leq y \leq 1-\epsilon, \\ C\sqrt{\frac{1-\epsilon}{\epsilon}} & \text{if } y > 1-\epsilon. \end{cases} \tag{4.3}$$

Since there is no drift term in this case $d^0(y) = 0$. This choice for the control function satisfies the following property.

Lemma 4.1 *Assuming $y \in [0, 1]$, by the choice of control function, (4.3), we have*

$$d^1(y)\sqrt{y(1-y)} \leq C.$$

Proof The proof follows directly from the choice of the control function. □

From here we assume that $y \in [0, 1]$ since in Sect. 4.4 we show that the new numerical scheme we introduce will always remain in the interval [0, 1].

4.2 Moro and Schurz method

In [25], Moro and Schurz developed a split step scheme that exploits the structure of a SDE so as to guarantee the numerical solution remains within the natural boundaries of the system. The scheme decomposes the SDE into two equations, a SDE and an ODE. This split is taken in such a way so that the exact solution or the conditional probability to the first equation (the SDE) is known. The exact solution to the first equation is then used as the initial condition for the ODE in that time step, which is integrated using any converging deterministic algorithm. The Moro and Schurz method can be used to obtain numerical solutions to the Wright-Fisher model for channel dynamics, [4], by splitting (2.3) as follows (where again the tildes have been removed from the parameters)

$$dy_1 = \frac{C^2(1-2y_1)}{4}dt + C\sqrt{y_1(1-y_1)}dW, \tag{4.4}$$

$$dy_2 = \left(A - \frac{C^2}{4} - \left(A + B - \frac{C^2}{2}\right)y_2\right)dt. \tag{4.5}$$

The first equation is equivalent to the Stratonovich SDE $dy_1 = C\sqrt{y_1(1-y_1)} \circ dW$ and so the analytic solution can be calculated (see [21], p. 120). This scheme ensures numerical solutions remain within [0, 1] providing $\frac{a}{a+b} \in [\frac{1}{2(N-1)}, 1 - \frac{1}{2(N-1)}]$, where a and b are the transition rates in the corresponding ion channel model, [4], which relate to the parameters A, B and C by (2.4). However, converting the SDE into the Stratonovich form introduces an extra term into the ODE part of the split, altering the dynamics of the ODE system and so preventing the scheme from preserving the boundaries for all parameter regimes. This limits the ability for incorporation into an electrophysiological model where the membrane potential varies over time and hence the parameters, which depend on the membrane potential, can take a wide range of values.

The scheme that we present below uses the Balanced Implicit Method to solve the SDE in the Moro and Schurz split scheme. The idea is to select the control functions so the BIM possesses ϵ-lifetime. ϵ is then taken as a function of the time step in such a way so as to ensure the approximation to the ODE remains within [0, 1]. Thus the scheme can be shown to possess eternal lifetime.

4.3 BISS method

The BISS method decomposes (2.3) into two equations, as in the Moro and Schurz method. The first is a SDE that consists of the diffusion term of (2.3) only. The second is an ODE that consists of the drift part and so (2.3) is separated into the following two equations

$$dy_1 = C\sqrt{y_1(1-y_1)}dW, \tag{4.6}$$

$$dy_2 = (A - (A + B)y_2)dt. \tag{4.7}$$

As in the Moro and Schurz method, the numerical solution to (4.6) is used as the initial condition in (4.7) with the solution to this second equation providing the approximation to the true solution at each time step. The main difference between the BISS method and the split step method of Moro and Schurz is the way in which the first equation is solved. The BISS method approximates the solution to (4.6) at each time step using the BIM, where the control functions are taken to be (4.3), so that the scheme possesses ϵ-lifetime. The second equation can be solved using any converging deterministic algorithm of at least order 1, and so the simplest method to use is the Euler method. Therefore the BISS method for (2.3) can be described by the following one step discretisation formula,

$$y_{n+1} = y_n + (A - (A + B)y_n)\Delta_t + \frac{C\sqrt{y_n(1 - y_n)}\Delta W_n}{1 + d^1(y_n)|\Delta W_n|}(1 - (A + B)\Delta_t). \tag{4.8}$$

Note that by definition $d^1(y_n) \geq 0$, providing $y_n \in [0, 1]$, since we assume $C > 0$. In the next section we shall prove that for all time, the BISS method does indeed remain within this interval, and so the denominator of the last term in (4.8) is always greater than or equal to one. Thus the numerical scheme for the BISS method, given by (4.8), will not become unstable, even for very small values of Wiener increments ΔW_n.

While in the standard sense of ϵ-lifetime the ϵ is constant, as discussed in [29], in the BISS method the ϵ is determined in terms of the discretisation time step Δ_t. In particular the ϵ is chosen to ensure that for a particular time step Δ_t, the numerical approximation to (4.7) is driven to a distance of ϵ away from the boundary, i.e. the numerical solution lies in the region $[\epsilon, 1 - \epsilon]$. This is always possible since A and B are strictly positive, so the drift of (2.3) pushes the solution away from the boundary. We take ϵ as

$$\epsilon = \min(A\Delta_t, B\Delta_t, 1 - A\Delta_t, 1 - B\Delta_t) > 0 \quad \text{when } \Delta_t \text{ sufficiently small.} \tag{4.9}$$

Such a choice will be shown to ensure that the discretisation scheme given by (4.8) possesses ϵ-lifetime.

4.4 Properties of the BISS method

We begin by proving a Lemma and a Theorem which together show that the BISS method possesses eternal lifetime as defined in Sect. 3. The Lemma is stated in [29], although no formal proof for the Lemma was given. From these two results it follows immediately that the first two moments of the discretisation scheme (4.8) are bounded, which we state as a Corollary.

Lemma 4.2 [29] *The BIM scheme for the Wright-Fisher model with no drift, where the control functions are taken to be* (4.3)*, possesses ϵ-lifetime.*

Proof First let us assume that at time t_n, $y_{n,1} \in [\epsilon, 1/2)$. The value at the next time step, according to the BIM scheme, is given by

$$y_{n+1,1} = \frac{y_{n,1} + C\sqrt{y_{n,1}(1-y_{n,1})}(\Delta W_n + |\Delta W_n|)}{1 + C\sqrt{(1-y_{n,1})/y_{n,1}}|\Delta W_n|}. \tag{4.10}$$

If $\Delta W_n \leq 0$ then

$$y_{n+1,1} = y_{n,1}\left(\frac{1}{1 + C\sqrt{(1-y_{n,1})/y_{n,1}}|\Delta W_n|}\right),$$

which is clearly non-negative and since $1 + C\sqrt{(1-y_{n,1})/y_{n,1}}|\Delta W_n| \geq 1$ hence $y_{n+1,1}$ lies in the interval $[0, 1/2)$. Otherwise

$$y_{n+1,1} = \frac{y_{n,1} + 2C\sqrt{y_{n,1}(1-y_{n,1})}|\Delta W_n|}{1 + C\sqrt{(1-y_{n,1})/y_{n,1}}|\Delta W_n|},$$

which is clearly non-negative. In order for $y_{n+1,1} \leq 1$ then the following inequality must hold

$$\left(\frac{1}{y_{n,1}} - 1\right) + \left(\frac{1}{y_{n,1}} - 2\right) C\sqrt{\frac{(1-y_{n,1})}{y_{n,1}}}|\Delta W_n| \geq 0.$$

Since $y_{n,1} < 1/2$ it follows that the inequality above is satisfied. Hence, given $y_{n,1}$ in $[\epsilon, 1/2)$ then $y_{n+1,1} \in [0, 1]$.

Now let us assume that $y_{n,1} \in [1/2, 1-\epsilon]$, then the value at the next time step is given by

$$y_{n+1,1} = \frac{y_{n,1} + C\sqrt{y_{n,1}/(1-y_{n,1})}((1-y_{n,1})\Delta W_n + y_{n,1}|\Delta W_n|)}{1 + C\sqrt{y_{n,1}/(1-y_{n,1})}|\Delta W_n|}. \tag{4.11}$$

If $\Delta W_n \geq 0$, (4.11) becomes,

$$y_{n+1,1} = \frac{y_{n,1} + C\sqrt{y_{n,1}/(1-y_{n,1})}|\Delta W_n|}{1 + C\sqrt{y_{n,1}/(1-y_{n,1})}|\Delta W_n|}. \tag{4.12}$$

This is clearly non-negative and it also follows that $y_{n+1,1}$ will be less than 1 since $y_{n,1} < 1$. Otherwise if $\Delta W_n < 0$ then (4.11) can be written as

$$y_{n+1,1} = \frac{y_{n,1} + C\sqrt{y_{n,1}/(1-y_{n,1})}(2y_{n,1} - 1)|\Delta W_n|}{1 + C\sqrt{y_{n,1}/(1-y_{n,1})}|\Delta W_n|}. \tag{4.13}$$

It follows directly that this is non-negative and for $y_{n+1,1} \leq 1$ the inequality

$$\left(\frac{1}{y_{n,1}} - 1\right) + 2\left(\frac{1}{y_{n,1}} - 1\right) C\sqrt{\frac{y_{n,1}}{1-y_{n,1}}}|\Delta W_n| \geq 0,$$

must hold. It is clear that this is true since $y_{n,1} < 1$, therefore if $y_{n,1} \in [1/2, 1-\epsilon]$ then $y_{n+1,1} \in [0, 1]$.

Thus if $y_{n,1} \in [\epsilon, 1-\epsilon]$, then $y_{n+1,1} \in [0,1]$ with probability 1 and so the BIM scheme for the Wright-Fisher model with no drift possesses ϵ-lifetime. □

Theorem 4.1 *The BISS scheme for the Wright-Fisher model possesses eternal lifetime.*

Proof In order to prove the BISS scheme possesses eternal lifetime we must show that $y_{n,2} = y_n \in [0,1]$ for all $n > 0$. By the previous Lemma we have that the solution to the first part of the split in the BISS method must remain in $[0,1]$ over a single time step, providing the initial condition is a distance ϵ away from the boundary. Therefore we must show that given the initial condition to the second equation in the split lies in $[0,1]$, then the choice of ϵ, (4.9), guarantees that the solution to this equation at each time step lies in the interval $[\epsilon, 1-\epsilon]$.

Let us assume that the initial condition to (2.3), y_0, lies in the interval $[\epsilon, 1-\epsilon]$, where ϵ is given by (4.9). Since $y_0 = y_{0,1}$ then by the previous Lemma it follows that $y_{1,1} \in [0,1]$, due to the ϵ-lifetime property of the BIM scheme for (4.6). Taking $y_{1,1}$ as the initial condition for the second equation in the split, (4.7), and using the Euler method to solve this equation, $y_{1,2}$ is given by

$$y_{1,2} = y_{1,1} + (A - (A+B)y_{1,1})\Delta_t. \tag{4.14}$$

For $y_{1,2} \in [\epsilon, 1-\epsilon]$, ϵ must be such that $\epsilon \leq \min(A\Delta_t, 1 - A\Delta_t, B\Delta_t, 1 - B\Delta_t)$, since the minimum and maximum values attained by $y_{1,1}$ are 0 and 1, respectively. By the definition of ϵ, (4.9), this inequality clearly holds. Therefore it follows that $y_{1,2} \in [\epsilon, 1-\epsilon]$. Since $y_1 = y_{1,2}$, we have that $y_1 \in [\epsilon, 1-\epsilon] \subset [0,1]$.

Now let us assume that $y_n \in [\epsilon, 1-\epsilon]$. Again it follows from the previous Lemma that $y_{n+1,1} \in [0,1]$ and so it remains to show that $y_{n+1,2} \in [\epsilon, 1-\epsilon]$ given that the initial condition to (4.7) is taken to be $y_{n+1,1}$. This follows immediately from the definition of ϵ, (4.9), as the Euler method is used to solve (4.7). Since $y_{n+1} = y_{n+1,2}$ we have that $y_{n+1} \in [\epsilon, 1-\epsilon]$.

Thus by induction it follows that given $y_0 \in [\epsilon, 1-\epsilon]$ we have with probability 1 $y_n \in [\epsilon, 1-\epsilon] \subset [0,1]$ for all $n > 0$ and so the BISS method possesses eternal lifetime. □

Note that in the above theorem we prove a slightly stronger condition than the definition of eternal lifetime given by Definition 3.1, namely that the BISS method ensures numerical solutions remain a distance ϵ away from the boundaries for all time and so lie within a subset of $[0,1]$.

Corollary 4.1 *The first two moments of the method* (4.8) *are bounded. That is there exist positive constants* $0 < G_2 \leq G_1 \leq 1$ *such that*

$$E(y_n) \leq G_1, \tag{4.15}$$

$$E(y_n^2) \leq G_2. \tag{4.16}$$

Proof The proof follows directly from the fact that (4.8) possesses eternal lifetime by the above Theorem, and so $y_n \in [0,1]$ for all $n > 0$. □

5 Strong convergence of the BISS method

The BIM method converges with strong order $1/2$ providing the drift and diffusion coefficients are Lipschitz continuous, [24]. The Moro and Schurz method converges with strong order 1 for weaker conditions on the drift and diffusion functions, namely that the drift coefficient is 3 times differentiable, the diffusion coefficient 4 times differentiable and the solution to the equation satisfies a certain moment bound. Extending these two results it is relatively straight forward to show that the BISS method converges with strong order $1/2$, under the assumption of Lipschitz continuous drift and diffusion coefficients. However, the diffusion coefficient in the Wright-Fisher model does not satisfy the Lipschitz condition on $[0, 1]$ and indeed it is not even differentiable at the end points of this interval. Therefore this proof of strong convergence breaks down.

In recent years a number of authors have tried to tackle the issue of convergence of certain numerical schemes when the diffusion coefficient fails to satisfy the Lipschitz condition [2, 14, 15], but this is still a little explored area. In [14] the authors use the Yamanda method, [19], to prove strong convergence of the Euler method for the CIR model, whose diffusion coefficient is only Hölder continuous, a weaker condition than Lipschitz continuity. Since the diffusion coefficient for the Wright-Fisher model satisfies the Hölder condition we shall use a similar approach to that presented in [14] to prove strong convergence of the BISS method.

For ease of notation we let $f(y) = A - (A + B)y$ and $g(y) = \sqrt{y(1-y)}$. In the convergence analysis we work with the integral form of (2.3),

$$Y(t) = Y_0 + \int_0^t f(Y(r))dr + \int_0^t Cg(Y(r))dW(r), \tag{5.1}$$

and the continuous approximation to (4.8), $y(t)$, defined for $t \in [t_n, t_{n+1})$

$$y(t) := y_n + f(y_n)(t - t_n) + \frac{Cg(y_n)(W(t) - W(t_n))}{1 + d^1(y_n)|\Delta W_n|}(1 - (A + B)\Delta_t), \tag{5.2}$$

where $\Delta W_n = W(t_{n+1}) - W(t_n)$, $\Delta_t = \Delta_{t_n} = t_{n+1} - t_n$ and $W(t)$ is a continuous Wiener process taking values $W(t_n), W(t_{n+1}), \ldots$ at the grid points. Defining $\overline{y}(t)$ and $\overline{W}(t)$ to be the following step functions

$$\overline{y}(t) := y_k \quad \text{for } t \in [t_k, t_{k+1}),$$

$$\overline{W}(t) := W(t_{k+1}) - W(t_k) \quad \text{for } t \in [t_k, t_{k+1}),$$

(5.2) can be re-written in the integral form

$$y(t) = y_0 + \int_0^t f(\overline{y}(r))dr + \int_0^t \frac{Cg(\overline{y}(r))(1 - (A + B)\Delta_t)}{1 + d^1(\overline{y}(r))|\overline{W}(r)|}dW(r). \tag{5.3}$$

Note that $y(t)$ is equal to $\overline{y}(t)$ at the discretisation points, $t = t_n$.

Lemma 5.1 *For all Δ_t sufficiently small*

$$\sup_{t\in[0,T]} E((y(t)-\overline{y}(t))^2) \le H\Delta_t, \tag{5.4}$$

where $H > 0$ is a constant independent of Δ_t.

Proof Letting $t \in [t_k, t_{k+1})$ and using the results of Corollary 4.1 and the fact that $1/(1+d^1(\overline{y}(r))|\overline{W}(r)|)^2 \le 1$, we have

$$\begin{aligned}
&E\left((y(t)-\overline{y}(t))^2\right)\\
&= E\left[\left(f(y_k)(t-t_k) + \frac{Cg(y_k)(1-(A+B)\Delta_t)(W(t)-W(t_k))}{1+d^1(y_k)|\Delta W_k|}\right)^2\right]\\
&\le 2\left(E\left[(f(y_k))^2(t-t_k)^2 + \frac{C^2(g(y_k))^2(1-(A+B)\Delta_t)^2(W(t)-W(t_k))^2}{(1+d^1(y_k)|\Delta W_k|)^2}\right]\right)\\
&\le 2\left(E\left[(f(y_k))^2\right]\Delta_t^2 + E\left[\frac{C^2(g(y_k))^2(1-(A+B)\Delta_t)^2}{(1+d^1(y_k)|\Delta W_k|)^2}\right]\Delta_t\right)\\
&\le H\Delta_t,
\end{aligned} \tag{5.5}$$

for some constant $H > 0$ independent of Δ_t. Finally taking the supremum over $0 \le t \le T$ we obtain the result of the Lemma. □

Following [14] we construct a sequence of twice continuosly differentiable smooth functions, $\phi_k(v)$, that approximate the function $|v|$. This approximation is then used to obtain an upper bound on the expectation of the absolute value between the true and the approximate solutions, $E|Y(t)-y(t)|$.

Letting $a_0 = 1$ and $a_k = e^{\frac{-k(k+1)}{2}}$, $k \ge 1$, then there exists a continuous function $\psi_k(v)$ with support in (a_k, a_{k-1}) such that

$$0 \le \psi_k(v) \le \frac{2}{kv}, \qquad a_k < v < a_{k-1} \quad \text{and} \quad \int_{a_k}^{a_{k-1}} \psi_k(u)du = 1.$$

Therefore the function

$$\phi_k(v) = \int_0^{|v|} dx \int_0^x \psi_k(u)du,$$

is twice continuously differentiable with the first two differentials satisfying the properties

$$|\phi_k'(v)| \le 1, \quad \forall v \in \mathbb{R}, \qquad |\phi_k''(v)| \begin{cases} \le \frac{2}{k|v|} & a_k < |v| < a_{k-1},\\ = 0 & \text{otherwise.}\end{cases} \tag{5.6}$$

Furthermore, ϕ_k satisfies the inequality

$$|v| - a_{k-1} \le \phi_k(v) \le |v|, \quad \forall v \in \mathbb{R}. \tag{5.7}$$

Theorem 5.1 *Let $Y(t)$ denote the true solution of (2.3), then for all Δ_t sufficiently small,*

$$\sup_{0\le t\le T} E|Y(t)-y(t)| \le e^{\lambda T}\left[a_{k-1}+\frac{C^2T}{k}\right] + e^{\lambda T}C^2T\Delta_t^{1/2}\left[\sqrt{H}\left(\frac{1}{ka_k}+\frac{\lambda}{C^2}\right)+\frac{2L}{ka_k}\right], \quad (5.8)$$

where $\lambda = A + B$ and $L > 0$ is a constant independent of Δ_t. Hence, it follows that

$$\lim_{\Delta_t\to 0}\sup_{0\le t\le T} E|Y(t)-y(t)| = 0.$$

Proof Letting $\lambda = A+B$, $\sigma(\overline{y}(r)) = 1-(1-\lambda\Delta_t)/(1+d^1(\overline{y}(r))|\overline{W}(r)|)$, and using (5.1) and (5.3) we have that

$$Y(t)-y(t) = -\lambda\int_0^t (Y(r)-\overline{y}(r))dr + C\int_0^t \left[g(Y(r))-g(\overline{y}(r))+\sigma(\overline{y}(r))g(\overline{y}(r))\right]dW(r).$$

Applying Itô's formula and using (5.6) we get

$$\begin{aligned} E\phi_k(Y(t)-y(t)) &= -\lambda E\int_0^t \phi_k'(Y(r)-y(r))(Y(r)-\overline{y}(r))dr \\ &\quad + \frac{C^2}{2}E\int_0^t \phi_k''(Y(r)-y(r))(g(Y(r))-g(\overline{y}(r)) \\ &\quad + \sigma(\overline{y}(r))g(\overline{y}(r)))^2 dr \\ &\le \lambda\int_0^t E|Y(r)-\overline{y}(r)|dr + \frac{C^2}{2}\mathrm{I}(t), \end{aligned}$$

where,

$$\begin{aligned} \mathrm{I}(t) &:= E\int_0^t \phi_k''(Y(r)-y(r))\left(g(Y(r))-g(\overline{y}(r))+\sigma(\overline{y}(r))g(\overline{y}(r))\right)^2 dr \\ &\le 2E\int_0^t \phi_k''(Y(r)-y(r))\left([g(Y(r))-g(\overline{y}(r))]^2+[\sigma(\overline{y}(r))g(\overline{y}(r))]^2\right)dr. \end{aligned}$$

Using Lemma 4.1 and the fact that

$$\max(g(\overline{y})) = 1/2 \quad \text{and} \quad 1/\left(1+d^1(\overline{y}(r))|\overline{W}(r)|\right) \le 1,$$

we have

$$(\sigma(\overline{y}(r))g(\overline{y}(r)))^2 \le C^2|\overline{W}(r)|^2 + C\lambda\Delta_t|\overline{W}(r)| + \frac{\lambda^2\Delta_t^2}{4}.$$

Therefore using (5.6)

$$
\begin{aligned}
&E\int_0^t \phi_k''(Y(r)-y(r))\,(\sigma(\overline{y}(r))g(\overline{y}(r)))^2\,dr\\
&\quad\le \int_0^t \frac{2}{ka_k}E\left(C^2|\overline{W}(r)|^2+C\lambda\Delta_t|\overline{W}(r)|+\frac{\lambda^2\Delta_t^2}{4}\right)dr\\
&\quad\le \left(C^2\Delta_t^{1/2}+C\lambda\Delta_t+\frac{\lambda^2\Delta_t^{3/2}}{4}\right)\frac{2t\Delta_t^{1/2}}{ka_k}\\
&\quad= p(\Delta_t^{1/2})\frac{2t\Delta_t^{1/2}}{ka_k},
\end{aligned}
\tag{5.9}
$$

where $p(\Delta_t^{1/2})$ is a polynomial in $\Delta_t^{1/2}$ with positive coefficients. Therefore for all Δ_t small enough,

$$p(\Delta_t^{1/2})<L,$$

for some constant $L>0$ independent of Δ_t. If follows that

$$E\int_0^t \phi_k''(Y(r)-y(r))(\sigma(\overline{y}(r))g(\overline{y}(r)))^2dr<\frac{2Lt\Delta_t^{1/2}}{ka_k}.$$

The function $g(y)=\sqrt{y(1-y)}$ is Hölder continuous with exponent $1/2$ and Hölder constant, $1/\sqrt{2}$. Using this fact along with (5.6) and Lemma 5.1

$$
\begin{aligned}
&E\int_0^t \phi_k''(Y(r)-y(r))\,(g(Y(r))-g(\overline{y}(r)))^2\,dr\\
&\quad\le \frac{1}{2}E\int_0^t \phi_k''(Y(r)-y(r))|Y(r)-y(r)|dr\\
&\qquad+\frac{1}{2}E\int_0^t \phi_k''(Y(r)-y(r))|y(r)-\overline{y}(r)|dr\\
&\quad\le \frac{1}{2}E\int_0^t \frac{2}{k}\mathbf{1}_{\{a_k<|Y(r)-y(r)|<a_{k-1}\}}dr+\frac{1}{2}E\int_0^t \frac{2}{ka_k}|y(r)-\overline{y}(r)|dr\\
&\quad\le \frac{t}{k}+\frac{t}{ka_k}\sqrt{H\Delta_t}.
\end{aligned}
$$

Therefore, for all Δ_t small enough the integral $\mathrm{I}(t)$ is bounded by,

$$\mathrm{I}(t)\le 2\left(\frac{t}{k}+\frac{t}{ka_k}\sqrt{H\Delta_t}+\frac{2Lt\Delta_t^{1/2}}{ka_k}\right)=:J(t).$$

Again using Lemma 5.1 we obtain,

$$E\phi_k(Y(t)-y(t)) \le \lambda \int_0^t E|Y(r)-y(r)|dr + \lambda \int_0^t E|y(r)-\overline{y}(r)|dr + \frac{C^2}{2}J(t)$$
$$\le \lambda \int_0^t E|Y(r)-y(r)|dr + \lambda t\sqrt{H\Delta_t} + \frac{C^2}{2}J(t).$$

From (5.7),

$$E\phi_k\left(Y(t)-y(t)\right) \ge E|Y(t)-y(t)| - a_{k-1}.$$

So

$$E|Y(t)-y(t)| \le a_{k-1} + \frac{C^2 t}{k} + \sqrt{H\Delta_t}\left(\frac{C^2 t}{ka_k} + \lambda t\right)$$
$$+ \frac{2C^2 Lt\sqrt{\Delta_t}}{ka_k} + \lambda \int_0^t E|Y(r)-y(r)|dr.$$

Applying the Grönwall inequality,

$$E|Y(t)-y(t)| \le e^{\lambda t}\left[a_{k-1} + \frac{C^2 t}{k}\right]$$
$$+ e^{\lambda t}C^2 t\Delta_t^{1/2}\left[\sqrt{H}\left(\frac{1}{ka_k} + \frac{\lambda}{C^2}\right) + \frac{2L}{ka_k}\right]. \tag{5.10}$$

Finally, taking the supremum over $0 \le t \le T$ gives (5.8).

For any $\delta > 0$, to prove the convergence we may choose $k \ge 1$ large enough such that

$$e^{\lambda T}\left[a_{k-1} + \frac{C^2 T}{k}\right] < \frac{1}{2}\delta, \tag{5.11}$$

and then choose $\Delta_t > 0$ small enough so that

$$e^{\lambda T}C^2\Delta_t^{1/2}T\left[\sqrt{H}\left(\frac{1}{ka_k} + \frac{\lambda}{C^2}\right) + \frac{2L}{ka_k}\right] < \frac{1}{2}\delta.$$

Therefore $\sup_{0\le t\le T} E|Y(t)-y(t)| < \delta$ and so $\lim_{\Delta_t\to 0}\sup_{0\le t\le T} E|Y(t)-y(t)| = 0$ as required. □

6 Numerical convergence of the BISS method

Numerical tests were performed to study the strong convergence of the BISS method for the Wright-Fisher model, (2.3), and a multidimensional form of this model involving 3 states. The 3 state system can be described by a system of two Itô SDEs,

$$dY_1 = (A_3 + (A_2 - A_3)Y_2 - (B_3 + B_1 + A_3)Y_1)\,dt - C_1\sqrt{Y_1Y_2}dW_1$$
$$+ C_2\sqrt{Y_1(1-Y_1-Y_2)}dW_2, \tag{6.1}$$

$$dY_2 = (A_1 + (B_1 - A_1)Y_1 - (A_2 + B_2 + A_1)Y_2)\,dt + C_1\sqrt{Y_1Y_2}dW_1 - C_3\sqrt{Y_2(1 - Y_1 - Y_2)}dW_3,$$

where Y_1, Y_2 are the proportion of alleles or channels in states 1 and 2 respectively and $1 - Y_1 - Y_2$ is the proportion in state 3.

As before this system is split into a SDE that consists of the diffusion part of (6.1) only and an ODE. The SDE is solved using the following one step discretisation scheme,

$$y_1^{n+1} = \frac{y_1^n - C_1\sqrt{y_1^n y_2^n}\Delta W_1^n + C_2\sqrt{(1 - y_1^n - y_2^n)y_1^n}\Delta W_2^n}{1 + D_1(\mathbf{y}^n) + D_2(\mathbf{y}^n) + D_3(\mathbf{y}^n)} + \frac{y_1^n(D_1(\mathbf{y}^n) + D_2(\mathbf{y}^n) + D_3(\mathbf{y}^n))}{1 + D_1(\mathbf{y}^n) + D_2(\mathbf{y}^n) + D_3(\mathbf{y}^n)},$$

$$y_2^{n+1} = \frac{y_2^n + C_1\sqrt{y_1^n y_2^n}\Delta W_1^n - C_3\sqrt{(1 - y_1^n - y_2^n)y_2^n}\Delta W_3^n}{1 + D_1(\mathbf{y}^n) + D_2(\mathbf{y}^n) + D_3(\mathbf{y}^n)} + \frac{y_2^n(D_1(\mathbf{y}^n) + D_2(\mathbf{y}^n) + D_3(\mathbf{y}^n))}{1 + D_1(\mathbf{y}^n) + D_2(\mathbf{y}^n) + D_3(\mathbf{y}^n)},$$

where the control functions are

$$D_1(\mathbf{y}) = \begin{cases} C_1\left(\sqrt{\frac{y_2}{y_1}} + \sqrt{\frac{\epsilon}{y_1 y_2}}\right)|\Delta W_1|, & \text{if } \epsilon < y_1 \le y_2, \\ C_1\left(\sqrt{\frac{y_1}{y_2}} + \sqrt{\frac{\epsilon}{y_1 y_2}}\right)|\Delta W_1|, & \text{if } \epsilon < y_2 < y_1, \end{cases}$$

$$D_2(\mathbf{y}) = \begin{cases} C_2\left(\sqrt{\frac{1-y_1-y_2}{y_1}} + \sqrt{\frac{\epsilon}{y_1(1-y_1-y_2)}}\right)|\Delta W_2|, & \text{if } 2y_1 + y_2 < 1, \\ C_2\left(\sqrt{\frac{y_1}{1-y_1-y_2}} + \sqrt{\frac{\epsilon}{y_1(1-y_1-y_2)}}\right)|\Delta W_2|, & \text{if } 2y_1 + y_2 \ge 1, \end{cases}$$

$$D_3(\mathbf{y}) = \begin{cases} C_3\left(\sqrt{\frac{1-y_1-y_2}{y_2}} + \sqrt{\frac{\epsilon}{y_2(1-y_1-y_2)}}\right)|\Delta W_3|, & \text{if } 2y_2 + y_1 < 1, \\ C_3\left(\sqrt{\frac{y_2}{1-y_1-y_2}} + \sqrt{\frac{\epsilon}{y_2(1-y_1-y_2)}}\right)|\Delta W_3|, & \text{if } 2y_2 + y_1 \ge 1. \end{cases}$$

If y_1 or y_2 are less than ϵ then set $y_i = \epsilon$ for $i = 1, 2$ respectively. Also if $y_1 + y_2 \ge 1 - \epsilon$ then set this sum equal to $1 - \epsilon$ in the above formulas.

The error between the true, $y_{true}(t)$ and the approximate solution $y_{approx}(t)$ at the final time, T, is considered. The "true" solution is calculated using the Euler-Maruyama method over a very fine time discretisation, namely with time step $\Delta_t = 2^{-9}$. We have chosen the parameter regime such that the solution lies far from the boundaries 0 and 1 and so the probability of the Euler-Maruyama approximation leaving the desired region is very small. Therefore instead of altering the scheme to ensure solutions remain within [0, 1], paths outside this interval are rejected. Since only a few paths will need to be rejected such an approach is computationally feasible, however this is not the case for all parameter regimes as we shall be discussed in the next section.

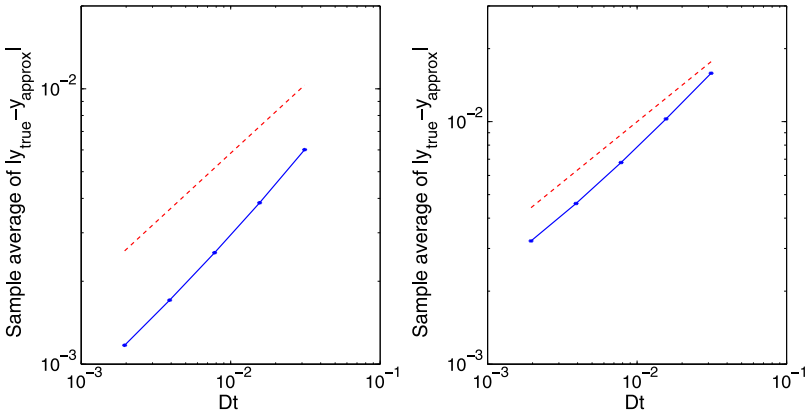

Fig. 1 (Color online) Log log plots showing the convergence results for Wright-Fisher models, (2.3) (*left*) and (6.1) (*right*). The *red dashed line* is a reference slope of $1/2$. The parameter values for (2.3) are $A = 1$, $B = 2$ and $C = 0.2462$ and for (6.1) $A_1 = 1$, $A_2 = 2$, $A_3 = 3$, $B_1 = 1.2$, $B_2 = 2.3$, $B_3 = 3.4$, $C_1 = 0.1271$, $C_2 = 0.1798$ and $C_3 = 0.1291$. The initial condition is taken to be the steady state of the deterministic part of (2.3) and (6.1)

We calculate the error,

$$E|y_{true}(T) - y_{approx}(T)| \tag{6.2}$$

between the "true" solution and a numerical approximation using the following five different time discretisations, $\Delta_t^k = 2^{k-1}$ for $1 \leq k \leq 5$ over a million simulations with final time $T = 1$, [13]. Results are given in Fig. 1.

The slopes of the errors appear to match well with the reference slope of $1/2$, Fig. 1, suggesting that the BISS method converges with strong order $1/2$ for both the one dimensional and multidimensional Wright-Fisher models, (2.3) and (6.1).

7 Application of the BISS method

7.1 Fixed voltage

The Hodgkin-Huxley model, [16], describes the propagation of an action potential (a rapid rise and fall in the cell membrane potential) through a squid giant axon. The change in membrane potential, V, over time is described in terms of the proportion of open sodium and potassium ion channels. The sodium channel is assumed to consist of three gates of type m and one of type h while the potassium channel is assumed to consist of four gates of type n, where each gate can be either open or closed. The proportion of open channels is thus given by the product of the proportion of open gates. Taking into account the stochastic behaviour of the ion channel, the proportion of open gates of type i can be approximated by the Wright-Fisher SDE as follows

$$di = (a_i(V) - (a_i(V) + b_i(V))i)\,dt + \sqrt{\frac{2(a_i(V) + b_i(V))}{(N_r - 1)}}\sqrt{(1-i)i}\,dW, \tag{7.1}$$

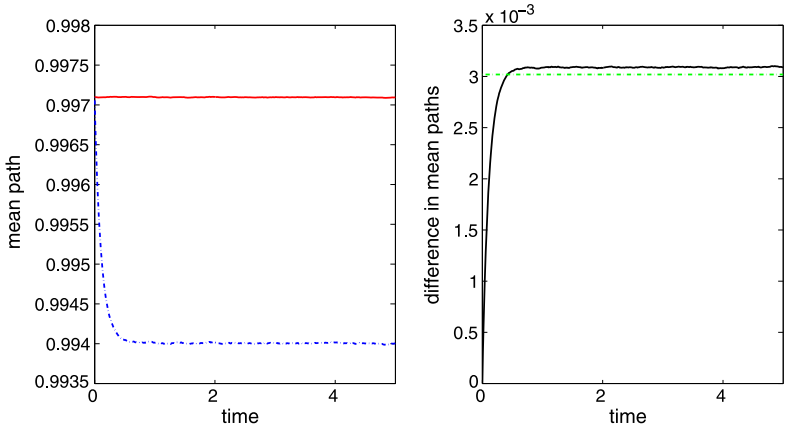

Fig. 2 (Color online) *Left*: Mean solution over a million simulations to (2.3) using the Euler-Maruyama method (*blue dot dash*) and the BISS method (*red solid line*). *Right*: Difference between the mean BISS method solution and the mean Euler-Maruyama solution over a million simulations (*black solid line*) and the mean of the difference between the mean paths (*green horizontal dot dash line*). The parameter values used for simulation are $a = 7.0064$, $b = 0.0204$, $N = 100$, $\Delta_t = 0.01$ and the initial condition is the steady state of the deterministic system. The maximum standard error for the BISS method is 2.8582×10^{-6} and for the Euler-Maruyama method it is 6.9183×10^{-6}

where N_r is the number of sodium or potassium channels, depending on the type of channel, and $a_i(V)$, $b_i(V)$ are the transition rates from closed to open and open to closed, respectively. These transition rates vary with the membrane potential according to the functions given in [4].

We consider the solution to (7.1) for the m gating variable of the sodium channel with fixed voltage, $V = 30$ mV, using the BISS method. This value of the voltage is attained near the height of the action potential. For this biologically relevant parameter regime the solution lies very close to the boundary 1, and so the chance that the Euler-Maruyama approximation leaves the interval [0, 1] is very high. In one million simulations, we observed that the Euler-Maruyama path left the desired region in over 700 000 simulations. Therefore if such paths were to be rejected, computing a mean solution using the Euler-Maruyama method over a large number of simulations would not be computationally feasible. Indeed this is not the common method employed in cardiac and neuronal cell stochastic simulation studies. Instead if the solution leaves this region at some time t, the Wiener increment is continually resampled until the approximation at that time lies within [0, 1]. Thus in practice the Euler-Mauryama scheme is altered to force the path to lie within a biologically realistic region, [7, 28]. To the best of our knowledge no convergence has been studied for the Euler-Maruyama method when such an alteration is performed, and it seems plausible that such an adjustment could potentially bias the numerical solution. Since the BISS method ensures solutions remain within [0, 1] without the need for any such alteration, we investigated the potential affect of this modification to the Euler-Maruyama method by comparing numerical solutions to (2.3) obtained using the BISS method with those of the adjusted Euler-Maruyama method.

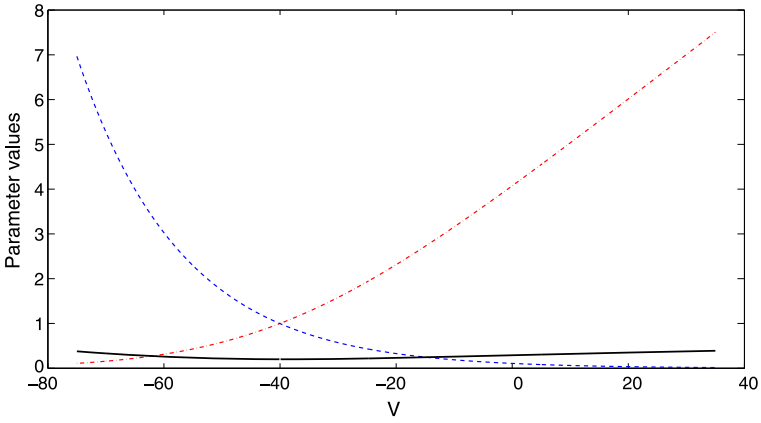

Fig. 3 (Color online) Parameter values for (2.3) over a biologically realistic voltage range. The *red dot dash line* is the parameter A, the *blue dash line* is the parameter B and the *black solid line* is the C parameter. All parameters are calculated for the m gate of the sodium channel in the Hodgkin-Huxley model according to the functions in [4]

In any single simulation, out of the one million simulations shown in Fig. 2, the maximum number of times the modification was utilised in the Euler-Maruyama implementation was 874. If the resampling of the Wiener increment did not bias the solution obtained using the Euler-Maruyama method then we would expect the difference between the two mean paths to fluctuate about 0. However, the Euler-Maruyama path is consistently smaller than the path obtained using the BISS method suggesting the effect of resampling the Wiener increment is to underestimate the solution to (2.3). Such effects are potentially important when the transition rates are no longer constant but are functions of time, as is the case when considering ion channel dynamics within the full Hodgkin-Huxley model.

7.2 Varying voltage

Finally we use the BISS method to solve the SDEs for the ionic currents in the full Hodgkin-Huxley model, [16], where the membrane potential varies over time according to the following differential equation

$$\frac{dV}{dt} = \frac{1}{C}\left(-G_N m^3 h(V - E_N) - G_K n^4 (V - E_K) - G_L(V - E_L) + I\right),$$

where the constants are as in [4]. The transition rates for the gating variables depend on the membrane potential, and so the parameters in (2.3) will also vary at each time step. In the Hodgkin-Huxely model the voltage varies between about -75 mV and 35 mV during an action potential. To illustrate the variation in the parameters for the ion channel equations over this voltage range, the values of A, B and C for the m gate Wright-Fisher approximation are shown in Fig. 3.

As previously mentioned, the BISS scheme ensures that the numerical approximation to (2.3) always lies a distance of ϵ away from the boundary, where ϵ depends

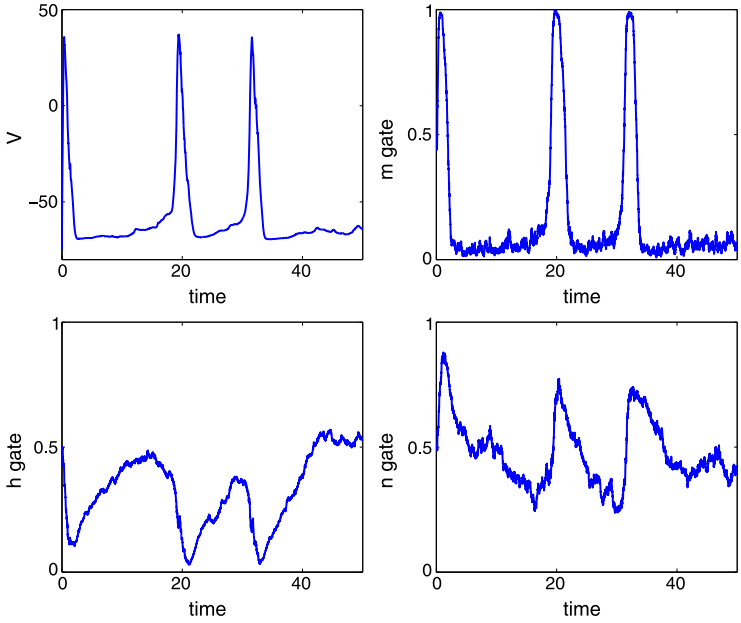

Fig. 4 Single realisation of the stochastic Hodgkin-Huxley model where the gating variables m, h and n are solved using the BISS method. The parameter values used for simulation are $\Delta_t = 0.01$, $N_{Na} = 100$ and $N_K = 33$ and the initial condition for the system is $V_0 = -75$, $m_0 = 0.5$, $h_0 = 0.5$ and $n_0 = 0.5$. The parameter values for the voltage equation are taken to be as in [4]

on the parameter values A, B and C. In the Hodgkin-Huxley model these parameters vary at every time step, and so the interval within which the solutions to the gating variable equations remain will also differ. Since the membrane potential remains bounded it is possible to calculate the range of values for ϵ that satisfy condition (4.9) within these voltage limits. Taking the minimum of these ϵ values, we are able to use a fixed value of ϵ in the numerical solution to the Hodgkin-Hulxey model, and so the interval within which the approximations lie will not vary over or between simulations.

Figure 4 shows a typical solution to this model where the SDEs for the variables, m, h and n are solved using the BISS method. Incorporating the Wright-Fisher formulation into the Hodgkin-Huxley model adds a level of complexity as the transition rates are changing at each time step due to the voltage dependence. However, the BISS method still ensures that numerical solutions remain within [0, 1] as shown in Fig. 4 while the Euler-Maruyama method utilises the resampling of the Wiener increment modification a maximum of 44 times in any of the one million simulations to ensure approximations lie within this interval.

8 Conclusion

In this paper we proposed a new numerical technique, the BISS method, that preserves the boundaries of the analytic solution to the Wright-Fisher model with muta-

tion, and the ion channel model modification (2.3). The idea is to split the equation into a SDE, consisting only of the diffusion coefficient and an ODE. The SDE is then solved using the BIM where the control functions are chosen so that the approximation remains within [0, 1] providing the solution at the previous time step is a distance ϵ away from the boundary. This ϵ is then determined as a function of the discretisation time step so that the approximation to the ODE always lies within the restricted interval $[\epsilon, 1-\epsilon]$. Therefore the numerical solution remains within [0, 1] with probability 1 for all time. Strong convergence of this scheme was proved and numerical experiments suggest that the order of convergence is $1/2$ for both the one dimensional and multidimensional systems. Solutions obtained using the BISS scheme were then compared with the Euler-Maruyama method where the Wiener increment is resampled to ensure solutions remain within [0, 1]. The BISS method was also used to solve the equations describing the ion channel dynamics in the Hodgkin-Huxley model where there is the added complication that the parameter values in the model change at each time step due to the voltage dependence. In this paper we have focused on the application of the BISS method to the Wright-Fisher model, however this method could also be applied to other problems in order to preserve the boundaries of solutions to SDEs.

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