LETTER TO THE EDITOR

Implementation Issues in Approximate Methods for Stochastic Hodgkin–Huxley Models

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INTRODUCTION

The article by Mino *et al.*[7] compares four different algorithms for implementing Hodgkin–Huxley models[6] with stochastic sodium channels: Strassberg and DeFelice (1993),[9] Rubinstein (1995),[8] Chow and White (1996),[3] and Fox (1997).[4] The first three algorithms utilize exact methods for describing channel kinetics with finite-state Markov process models. In contrast, the algorithm of Fox uses stochastic differential equations (SDEs) to approximate the Markov process models. In addition to being simpler, the approximate method of Fox is around 7 times faster than the Chow & White algorithm, the fastest of the exact methods.[7] However, for simulations of a patch of membrane with 1,000 sodium channels, Mino *et al.*[7] reported that the approximate method of Fox produced quite different action potential (AP) statistics than the other methods. They consequently argued that, in spite of its computational advantage, the Fox algorithm may be too inaccurate in some circumstances to use reliably as an approximation to the exact methods. In repeating the simulations of Mino *et al.*,[7] I have found that some (but not all) of the inaccuracies that they reported were due to aspects of their implementation of the Fox algorithm, and that these inaccuracies become practically insignificant with an alternative implementation of the algorithm.

IMPLEMENTATION OF THE FOX METHOD

The three algorithms utilizing finite-state Markov process models all produce an integer number of open sodium channels N_{Na} at each time step of the simulation. In contrast, the Fox SDEs produce a real-number estimate of the fraction of open sodium activation m and inactivation h particles at each time step. The number of open sodium channels is then estimated to be [Eq. (9) of Ref. 7]

$$N_{\mathrm{Na}}(t) = N_{\mathrm{Na}}^{\max} m^3(t) h(t), \qquad (1)$$

where $N_{\mathrm{Na}}^{\max}$ is the total number of sodium channels in the patch of membrane.

In Mino and colleagues' implementation of the Fox algorithm, all values of $N_{\mathrm{Na}}(t)$ calculated with Eq. (1) are *rounded down* to the nearest integer, to be consistent with the integer values produced by the Markov process models (Hiroyuki Mino, pers. comm.). However, in deterministic Hodgkin–Huxley models the number of open channels is left as a real number, without any rounding, and Fox and colleagues do not mention any rounding in the implementation of their algorithm.[4,5] AP generation in Hodgkin–Huxley models is highly dependent on the number of open sodium channels and consequently may be sensitive to any rounding of $N_{\mathrm{Na}}(t)$. In particular, rounding *down* may produce an elevation in the threshold current and an increase the spike latency. Consequently, I believe that, if rounding is to be applied to $N_{\mathrm{Na}}(t)$ in the Fox algorithm, it would be more accurate to round to the *nearest* integer.

SIMULATIONS

I implemented the Chow & White and Fox algorithms and repeated the simulations of Mino *et al.*,[7] comparing the results obtained with the two different methods for rounding $N_{\mathrm{Na}}(t)$ in the Fox method. Rounding down is indicated by the mathematical 'floor' operation $\lfloor \cdot \rfloor$ and rounding to the nearest integer by the 'nearest integer' operation $\mathrm{nint}(\cdot)$.

A number of stimulus and model parameter values were misreported in Ref. 7; all values for current amplitudes given in Ref. 7 need to be divided by 0.265 to obtain the correct values, and corrected model parameter values are provided in Table 1 (Hiroyuki Mino, pers. comm.). Note that the corrected value for E_{Na} is necessary because the equations in Ref. 7 are given in terms of the membrane potential relative to the resting potential $V_{\mathrm{rest}} = -78$ mV (Hiroyuki Mino, pers. comm.). All simulations were performed with a sampling step of 1 μs.

Responses to two different stimuli are investigated, a simple monophasic current pulse and a preconditioned monophasic current pulse, as illustrated in Fig. 1(a) and (b), respectively, of Ref. 7. Here I give the current amplitudes in terms of their actual values,

Model parameter	Value
C_m	0.0714 pF
R_m	1953.49 MΩ
E_{Na}	144 mV

corresponding to corrected values for the current amplitudes reported in Ref. 7. A subset of simulation results are given in the next section, in order to illustrate the effects of rounding $N_{Na}(t)$ on the AP statistics.

RESULTS

Figure 1 shows simulation results for the simple monophasic pulse as a function of stimulus current, corresponding to Fig. 3 of Ref. 7. The firing efficiency (FE) refers to the fraction of trials in which an AP is generated. The FE versus current amplitude curves plotted in the top panel can be characterized by fitting an integrated Gaussian function.[2] This function can be
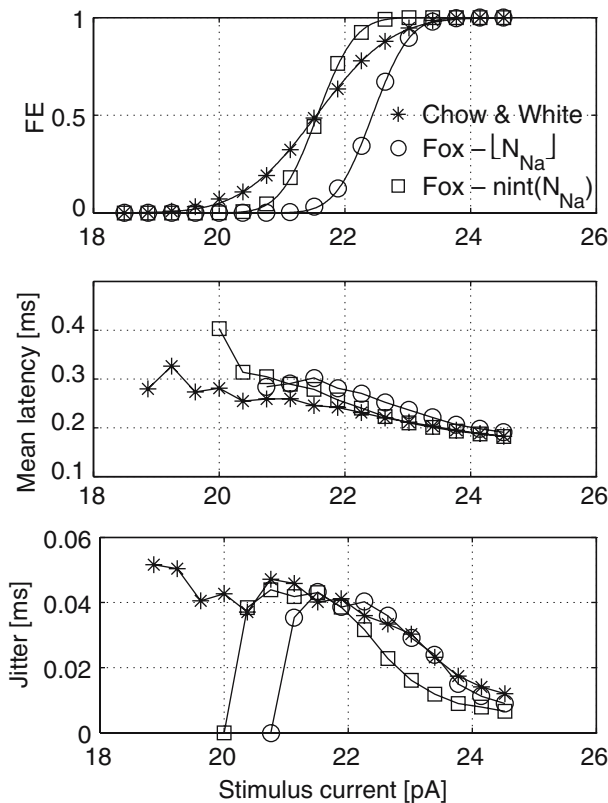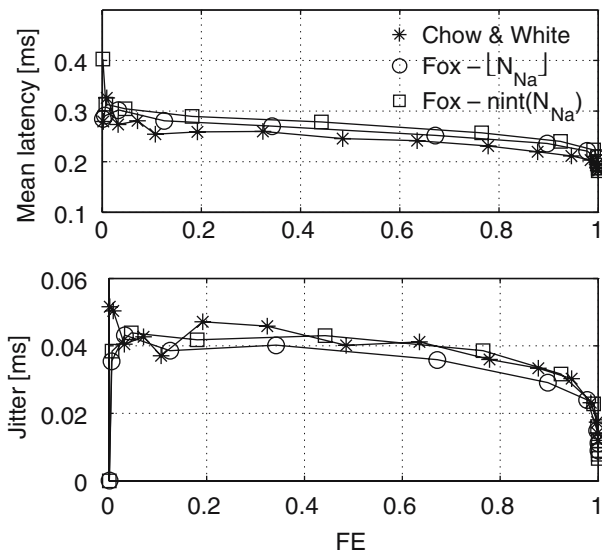

FIGURE 1.   Firing efficiency (top), mean latency (middle) and jitter (bottom) versus stimulus current for a monophasic pulse of duration 100 μs for three different algorithms: the Chow & White algorithm (*), the Fox algorithm with rounding down of $N_{Na}(t)$ (○), and the Fox algorithm with rounding of $N_{Na}(t)$ to the nearest integer (□).

parameterized by the threshold current I_{th}, which is the current amplitude corresponding to an FE of 0.5, and the relative spread (RS), which is a normalized measure of the dynamic range of the curve (the shallower the slope, the larger the value of RS, and the steeper the slope, the smaller the value of RS). The threshold current $I_{th} = 22.44$ pA for the Fox algorithm with nint $\lfloor N_{Na}(t) \rfloor$ (i.e., rounding down) is substantially higher than the value of $I_{th} = 21.55$ pA for the Chow & White algorithm, as reported by Mino et al.[7] In contrast, $I_{th} = 21.57$ pA for the Fox algorithm with nint($N_{Na}(t)$) (i.e., rounding to the nearest integer) is very close to the value for the Chow & White algorithm. However, it appears that the method for rounding $N_{Na}(t)$ has negligible effect on the relative noise level of the threshold fluctuations in the Fox algorithm; the slopes of the Fox curves are both steeper than the slope for the Chow & White algorithm. The values of RS for the Chow & White algorithm, the Fox algorithm with $\lfloor N_{Na}(t) \rfloor$, and the Fox algorithm with nint($N_{Na}(t)$) are 0.0437, 0.0208, and 0.0217, respectively. Thus, the observation that for this stimulus the Fox RS value is only around half that of the Chow & White RS value indicates a true inaccuracy of the Fox approximation.

The mean spike latency for the three different algorithms is plotted as a function of stimulus current in the middle panel of Fig. 1. The mean latency for the Fox algorithm with $\lfloor N_{Na}(t) \rfloor$ is longer than that of the Chow & White algorithm at all stimulus currents, although the values do begin to converge at the higher stimulus amplitudes. The mean latency for the Fox algorithm with nint($N_{Na}(t)$) is also longer than that of the Chow & White algorithm for lower stimulus currents, but above ~ 22.5 pA the values converge.

The standard deviation in the spike latency, referred to as the 'jitter', is plotted as a function of stimulus current in the bottom panel of Fig. 1. Note that at lower stimulus currents that produce very few APs, estimates of the jitter are unreliable, but as the FE increases the estimates rapidly become more reliable. The jitter for the Fox algorithm with $\lfloor N_{Na}(t) \rfloor$ is very similar to that of the Chow & White algorithm at all stimulus currents for which a reliable estimate can be obtained. The jitter for the Fox algorithm with nint($N_{Na}(t)$) is also similar to that of the Chow & White algorithm up to the stimulus current around I_{th} for the two algorithms, but at higher stimulus currents (corresponding to FE > 0.5) the Fox algorithm exhibits lower jitter than the Chow & White algorithm.

Some of the differences in mean latency and jitter predicted by the different algorithms may be a byproduct of the mismatch in firing efficiencies produced by the models at the various stimulus currents. To test this, the mean latency and jitter are replotted in

FIGURE 2. Mean latency (top) and jitter (bottom) versus firing efficiency for a monophasic pulse of duration 100 μs for three different algorithms: the Chow & White algorithm (*), the Fox algorithm with rounding down of $N_{Na}(t)$ (○), and the Fox algorithm with rounding of $N_{Na}(t)$ to the nearest integer (□).

Fig. 2 as a function of FE, rather than stimulus current. It can be seen that when the stimulus amplitude is adjusted for each algorithm such that they all produce

the same FE, fairly similar mean latencies and jitters are observed.

Figure 3 shows simulation results for the 'preconditioned' monophasic pulse, corresponding to the top panel of Fig. 4 of Ref. 7. The mean spike latency (LT) of 0.648 ms for the Fox algorithm with $\lfloor N_{Na}(t) \rfloor$ is much longer than the value of 0.497 ms for the Chow & White algorithm, as reported by Mino *et al.*[7] However, the Fox algorithm with nint($N_{Na}(t)$) has a mean spike latency of 0.520 ms, which is much closer to the value for the Chow & White algorithm. Again, it appears that the method for rounding $N_{Na}(t)$ has little effect on the relative noise level of the threshold fluctuations in the Fox algorithm; the spike jitter (JT) for the Fox algorithm is much smaller that the jitter for the Chow & White algorithm, irrespective of the method of rounding $N_{Na}(t)$.

In the simulations above, the threshold current and mean spike latency are affected by rounding $N_{Na}(t)$, and consequently one could expect to see the same effects in the deterministic equivalent of the Fox equations (i.e., the original Hodgkin–Huxley[6] ordinary differential equation formulation for the gating particles). Fig. 4 illustrates that this is indeed the case. The deterministic model with $\lfloor N_{Na}(t) \rfloor$ only generates an AP in response to the 100-μs monophasic pulse following the 500-μs preconditioning current, whereas for
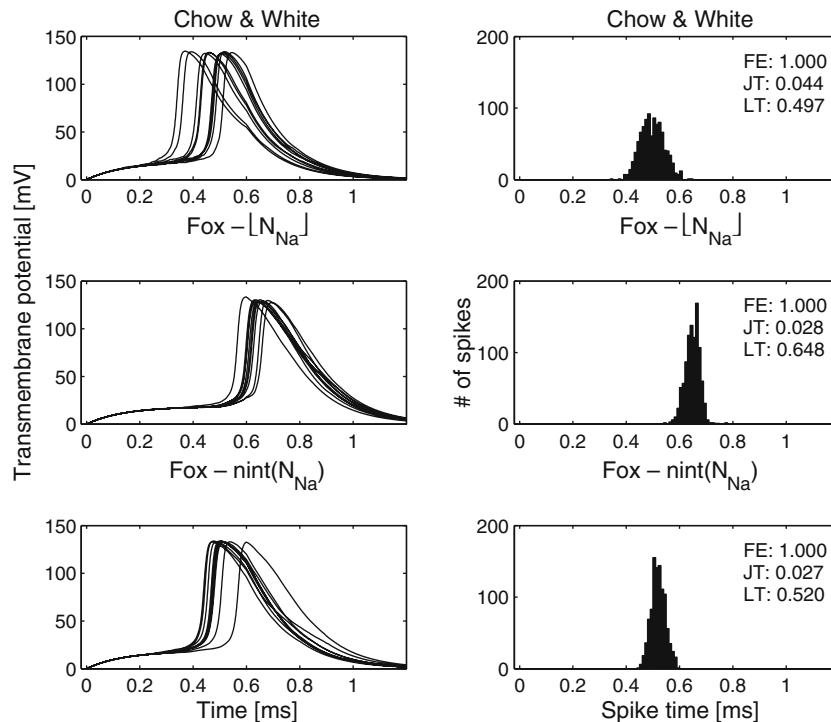
FIGURE 3. Example transmembrane potentials in response to 10 identical preconditioned monophasic pulse stimuli (left). Histograms of spike times for 1,000 trials (right). The insets to the histograms give the respective firing efficiency (FE), jitter (JT) and mean latency (LT) for the 1,000 trials. A preconditioning current of 9.434 pA was applied for 500 μs, followed immediately by a current of 13.208 pA for 100 μs.
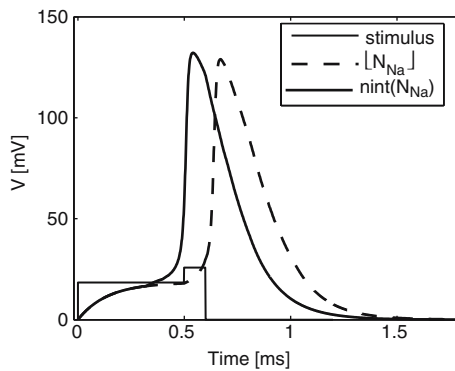
FIGURE 4. Transmembrane potentials from the deterministic equivalent to the Fox model in response to the preconditioned monophasic pulse stimuli.

nint($N_{Na}(t)$) an AP is generated before the end of the 'preconditioning' current, producing a much shorter latency. Mino *et al.*[7] referred to the preconditioning current as being subthreshold, but my simulation results show that this is only true in the case of $N_{Na}(t)$ being rounded down.

DISCUSSION

The results of my simulations indicate that several of the inaccuracies of the Fox algorithm described by Mino *et al.*[7] resulted from their choice of rounding down the number of open sodium channels at each simulation time step, rather than rounding to the nearest integer. I also performed some simulations without any rounding of $N_{Na}(t)$. The results were similar to those for rounding to the nearest integer, but the closest results to the Chow & White algorithm were nevertheless obtained with rounding to the nearest integer, suggesting that the correct rounding operation in the Fox algorithm can benefit its accuracy. However, several inaccuracies were still present in the simulation results described above. It appears that these may all result from underestimation of the relative noise level of the threshold fluctuations. We are currently investigating the source of this inaccuracy and developing methods to correct it.[1]

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