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Physica A 351 (2005) 427–438

PHYSICA A

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Time to first spike in stochastic Hodgkin–Huxley systems

Henry C. Tuckwell^{a,b,*}, Frederic Y.M. Wan^c

^a*Department of Mathematics, University of California San Diego La Jolla, CA 92093, USA*

^b*Max Planck Institute for Mathematics in the Sciences, Inselstr. 22, Leipzig D-04103, Germany*

^c*Department of Mathematics, University of California Irvine, Irvine, CA 92697, USA*

Received 23 September 2004; received in revised form 19 November 2004

Available online 25 December 2004

Abstract

The time to first spike is an experimentally observed quantity in laboratory experiments. In the auditory, somatic and visual sensory modalities, the times of first spikes in the corresponding cortical neurons have been implicated as coding much of the information about stimulus properties. We describe an analytical approach for determining the time to first spike from a given initial state which may be applied to a general nonlinear stochastic model neuron. We illustrate with a standard Hodgkin–Huxley model with a Gaussian white-noise input current whose drift parameter is μ and whose variance parameter is σ . Partial differential equations (PDEs) of second order are obtained for the first two moments of the time taken for the depolarization to reach a threshold value from rest state, as functions of the initial values. Simulation confirms that for small noise amplitudes a 2-component model is reasonably accurate. For small values of the noise parameter σ , including the deterministic case $\sigma = 0$, perturbation methods are used to find the moments of the firing time and the results compare favorably with those from simulation. The approach is accurate for almost all σ when μ is above threshold for action potentials in the absence of noise and over a considerable range of values of σ when μ is as small as 2. The same methods may be applied to

*Corresponding author. Department of Mathematics, University of California San Diego La Jolla, CA 92093, USA. Tel.: +1 858 534 5863; fax: +1 858 452 9848.

E-mail addresses: htuckwel@math.ucsd.edu, tuckwell@mis.mpg.de (H.C. Tuckwell).

models similar to Hodgkin–Huxley which involve channels for additional or different ionic currents.

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Keywords: Stochastic neuron model; Hodgkin–Huxley

1. Introduction

Understanding the manner in which nervous systems transmit information has been a challenge since the original observation that the rate of spiking seemed to portray features of an eliciting stimulus [1]. It subsequently became clear that such “rate codes” would in many situations be inefficient and unreliable compared with schemes where information was transmitted by the times or sets of times at which spikes occurred [2]. Such conjectures, which are difficult to test scientifically, have been discussed in numerous articles in the last 7 or so years (see for example Ref. [6] for several references). Many authors have recently proposed that the first spikes which occur in, for example, cortical neurons or groups of them, contain a major portion of information about a stimulus. Thus, the determination of the time to first spike in a quiescent neuron is relevant to the information content in a train as a result of stimulation. This has been elucidated on for several sensory modes including auditory [3–5], visual [6] and somatic [7]. Although the appearance of spikes in a cortical neuron is dependent on a chain of events [14, Chapter 10], the time to first spike is a function of the time at which an (assumed) trigger zone becomes sufficiently depolarized to give rise to an action potential, which is the quantity we set out to determine in the present article.

The many recent investigations of stochastic dynamical models of single neurons [8–12] are thus expected to lead to a better understanding of the details of certain cognitive aspects of the activity of the mammalian central nervous system [13]. However, apart from the complexity of their electrochemical processes, the dynamical behavior of neurons has three features which makes its mathematical description and analysis difficult. These consist of their nonlinear behavior, the fact that they are spatially distributed and the stochastic nature of both their input and output processes. In essence therefore, they may be characterized by means of nonlinear systems of stochastic partial differential equations.

A number of previous researches have focused on classical simplified one-dimensional models which lead to the subthreshold potential being represented as an Ornstein–Uhlenbeck process (OUP) [14]. In the OUP model the subthreshold behavior is linear but in order to determine accurately the firing activity of the neuron, the time of first passage of the potential to threshold must be determined. The moments of the firing time can be found analytically, but its probability density function, which may be found by solving partial differential equations (PDEs) numerically, is most easily estimated by simulation of solutions of the membrane potential stochastic differential equations. Despite these advances, such models suffer from several shortcomings: not only do they collapse the entire neuronal

structure, including soma, dendrites and axon, into a single space point (or equivalently assume no spatial variation of potential throughout the neuron), but they also incorporate an artificially imposed threshold and reset mechanism which are known to be inaccurate. It is desirable to consider more realistic dynamical models such as that of Hodgkin and Huxley [15], which is an underlying model employed in the current article. Nevertheless, in this work we do not take into account the spatial extent of the neuron.

For the related nonlinear Fitzgugh–Nagumo model, there have been many simulation and semi-analytical studies [16–18], with a view to exploring certain phenomena of interest such as stochastic resonance and stochastically induced oscillations. Only recently was an analytical approach employed in order to ascertain the statistical properties of the time interval to firing [19]. Similarly for Hodgkin–Huxley models with noise, although some features of spiking activity have been investigated [11,20–24], there have been no analytical attempts to determine time to the first spike firing or the interspike interval. In this paper, we extend our previous work on the Fitzgugh–Nagumo model using similar techniques for the space-clamped Hodgkin–Huxley system. Thus, we attempt to solve approximately partial differential equations satisfied by the moments of the first exit time for the relevant 4-component Markovian diffusion process. The problem of determining the interspike interval is not as straightforward but is discussed using a heuristic approach in a recent article [25].

2. The stochastic dynamical model

A general differential equation for the voltage of a space-clamped neuron with N types of ion channels where the k th species has n_k gating variables and a maximal conductance of \bar{g}_k can be written

$$C \frac{dV}{dt} = - \sum_{k=1}^N \bar{g}_k (V - V_k) \prod_{j=1}^{n_k} \gamma_{kj}^{m_{kj}} + I(t), \quad (1)$$

where I is any applied current that could be experimental or naturally synaptic. This equation is gleaned from measurements on many neurons which have led to a more complex dynamics than the basic potassium and sodium ion channels in the pioneering Hodgkin–Huxley [15] model, as for example those in certain cells of the hippocampus [26] and auditory brainstem [27]. The $[0, 1]$ -valued variables γ_{kj} , $k = 1, \dots, N; j = 1, \dots, n_k$ are assumed to satisfy the first-order equations

$$\frac{d\gamma_{kj}}{dt} = \alpha_{kj}(1 - \gamma_{kj}) - \beta_{kj}\gamma_{kj}, \quad (2)$$

where the α_{kj} 's and β_{kj} 's depend on V . If the applied current is, for example, Gaussian white noise, the theory of Markov processes may be applied to the system of equations (1) and (2). However, it is expeditious to demonstrate with a classical and relatively simple system.

We therefore study the empirically based Hodgkin–Huxley [15] with additive Gaussian white-noise current as first considered in Ref. [28]. The white noise is used as an approximation to Poisson trains of excitatory and inhibitory post-synaptic potentials, representing the input to a given cell at various synaptic terminals over the somadendritic surface. With such a current, the state of the neuron is described by the following system of stochastic differential equations:

$$dV = \frac{1}{C}\{\mu + \bar{g}_K n^4(V_K - V) + \bar{g}_{Na} m^3 h(V_{Na} - V) + g_l(V_l - V)\}dt + \sigma dW \tag{3}$$

$$dn = [\alpha_n(1 - n) - \beta_n n]dt,$$

$$dm = [\alpha_m(1 - m) - \beta_m m]dt,$$

$$dh = [\alpha_h(1 - h) - \beta_h h]dt,$$

where C is the membrane capacitance in $\mu\text{F}/\text{cm}^2$, V is the depolarization from resting membrane potential in mV and V_K and V_{Na} are the Nernst equilibrium potentials (mV) for potassium and sodium ions. The quantities \bar{g}_K and \bar{g}_{Na} are the assumed fixed maximal membrane conductances, in mS/cm^2 , for potassium and sodium. The dimensionless $[0, 1]$ -valued dynamical variables n, m and h represent, respectively, the fractions of potassium channel activation, sodium channel activation and sodium channel inactivation. The standard coefficients and constants are reproduced in the appendix.

Solution of the corresponding deterministic system, with $(\sigma = 0)$ using Runge–Kutta methods, reveals [29] that there is a threshold current of about $\mu = 4.15$ required to elicit a single spike and that a sustained current of about $\mu = 6.5$ elicits a regular train of impulses. As μ increases further, the spike frequency increases while the amplitude of the spikes decreases. We wish to determine the time to elicit a spike using first exit time theory for diffusion processes.

Using our previous notation [28], the backward Kolmogorov equation satisfied by the transition probability density function $p(v, x, y, z, t; \hat{v}, \hat{x}, \hat{y}, \hat{z}, \hat{t})$ of the 4-dimensional process (V, X, Y, Z) , where X is the potassium activation variable n , Y is the sodium activation variable m , and Z is the sodium inactivation variable h , and where $\hat{v}, \hat{x}, \hat{y}, \hat{z}, \hat{t}$ are backward (earlier) variables, is

$$\begin{aligned} -\frac{\partial p}{\partial \hat{t}} = & \frac{\sigma^2}{2} \frac{\partial^2 p}{\partial \hat{v}^2} + \{c_1(V_K - \hat{v})\hat{x}^4 + c_2(V_{Na} - \hat{v})\hat{y}^3 \hat{z} + c_3(V_l - \hat{v}) + \mu\} \frac{\partial p}{\partial \hat{v}} \\ & + \{\alpha_n(\hat{v})(1 - \hat{x}) - \beta_n(\hat{v})\hat{x}\} \frac{\partial p}{\partial \hat{x}} + \{\alpha_m(\hat{v})(1 - \hat{y}) - \beta_m(\hat{v})\hat{y}\} \frac{\partial p}{\partial \hat{y}} \\ & + \{\alpha_h(\hat{v})(1 - \hat{z}) - \beta_h(\hat{v})\hat{z}\} \frac{\partial p}{\partial \hat{z}}, \end{aligned} \tag{4}$$

where $c_1 = \bar{g}_K/C$, $c_2 = \bar{g}_{Na}/C$ and $c_3 = g_l/C$.

It is useful to define the differential operator \hat{L} so that this PDE can be written

$$-\frac{\partial p}{\partial \hat{t}} = \hat{L}p.$$

If the initial value of (V, X, Y, Z) is in fact $(\hat{v}, \hat{x}, \hat{y}, \hat{z})$ and this point lies in the 4-dimensional set A then the n th moments $M_n(\hat{v}, \hat{x}, \hat{y}, \hat{z}), n = 0, 1, 2, \dots$, of the exit time of the 4-dimensional process from A , are the solutions of the recursive system of partial differential equations $\hat{L}M_n = -nM_{n-1}$, with boundary conditions that for $n \geq 1$, M_n vanish on regular boundaries of A [32] and for $n = 0$, that $M_n = 1$ on the boundary of A . (Boundary classification for multidimensional diffusion processes proceeds as for one-dimensional processes but is more difficult to accomplish explicitly.) In particular, if we denote the time of first passage of the process (V, X, Y, Z) with initial value $\hat{v}, \hat{x}, \hat{y}, \hat{z}$, in some subthreshold set A^* where $\hat{v} < v_\theta$ to suprathreshold values, where $\hat{v} > v_\theta$ by $T_1(\hat{v}, \hat{x}, \hat{y}, \hat{z}; v_\theta)$ with expected value $E(T_1) = F(\hat{v}, \hat{x}, \hat{y}, \hat{z}; v_\theta)$ and second moment $E(T_1^2) = G(\hat{v}, \hat{x}, \hat{y}, \hat{z}; v_\theta)$, then we have

$$\hat{L}F = -1 \tag{5}$$

and

$$\hat{L}G = -2F, \tag{6}$$

which must be solved with appropriate boundary conditions.

2.1. Two-component system

Since solving the 4-dimensional system is rather complicated, we seek, for appropriate parameter values, to reduce the problem to a 2-dimensional one. We may sometimes employ a 2-dimensional approximation to the Hodgkin–Huxley system since it is often found (analogously to the Fitzhugh–Nagumo system) that the trajectory of the phase point prior to a spike entails major changes in the variables V and m (now designated Y) but that during the same epoch the variables n and h (X and Z) are practically unchanged. Thus this reduction technique may be used to determine approximately the time to the first spike, but not the time interval between the first and subsequent spikes.

In the 2-component model, the values of n and h are held fixed at their initial values, denoted now by n_0 and h_0 , thus eliminating two differential equations. Thus, we consider the two-component approximation (\bar{V}, \bar{m}) satisfying the stochastic differential equations

$$\begin{aligned} d\bar{V} &= \frac{1}{C}\{[\mu + \bar{g}_K n_0^4(V_K - \bar{V}) + \bar{g}_{Na} \bar{m}^3 h_0(V_{Na} - \bar{V}) + g_I(V_I - \bar{V})]dt + \sigma dW\} \\ d\bar{m} &= [\alpha_{\bar{m}}(1 - \bar{m}) - \beta_{\bar{m}}\bar{m}]dt, \end{aligned} \tag{7}$$

where $\alpha_{\bar{m}}$ and $\beta_{\bar{m}}$ take the same form as α_m and β_m .

Dropping bars on \hat{v} and \hat{y} , denote the time of first passage of the process $(\bar{V}, \bar{m}) = (\bar{V}, \bar{Y})$ with initial value (\hat{v}, \hat{y}) in an open rectangle $(v^*, v_\theta) \times (0, 1)$ to $\hat{v} > v_\theta$ (where v^* is a suitable value of the voltage at a sufficiently hyperpolarized state) by $\bar{T}_1(\hat{v}, \hat{y}; v_\theta)$

with expected value $E(\bar{T}_1) = \bar{F}(\hat{v}, \hat{y}; v_\theta)$ and second moment $E(\bar{T}_1^2) = \bar{G}(\hat{v}, \hat{y}; v_\theta)$. Then we have

$$\hat{L}_1 \bar{F} = \frac{\sigma^2}{2} \frac{\partial^2 \bar{F}}{\partial \hat{v}^2} + \{c_1(V_K - \hat{v})n_0^4 + c_2(V_{Na} - \hat{v})\hat{y}^3 h_0 + c_3(V_l - \hat{v}) + \mu\} \frac{\partial \bar{F}}{\partial \hat{v}} + \{\alpha_m(\hat{v})(1 - \hat{y}) - \beta_m(\hat{v})\hat{y}\} \frac{\partial \bar{F}}{\partial \hat{y}} = -1,$$

which defines \hat{L}_1 . The second moment \bar{G} satisfies $\hat{L}_1 \bar{G} = -2\bar{F}$.

3. Methods of solution

The systems of stochastic differential (3) or (7) may be simulated using a standard Euler method [32]. We show in Fig. 1 the sample paths for the deterministic case, $\sigma = 0$, for $\mu = 10$, in the two and four component models. Similarly, in Fig. 2, we show 10 sample paths for both the two and four component models for $\mu = 15$ and $\sigma = 1.5$.

It can be seen that the envelopes containing the paths in each case are not dissimilar, indicating that for the present problem the two-component approximation should be reasonably accurate provided the standard deviation is not too large relative to the mean. That the times to first spike have similar distributions is seen in Fig. 3 (in all cases the threshold depolarization is set at 15 mV from resting level). It is noted that in the two-component model there is no recovery but that the rising phase of V is similar to that in the 4-component system.

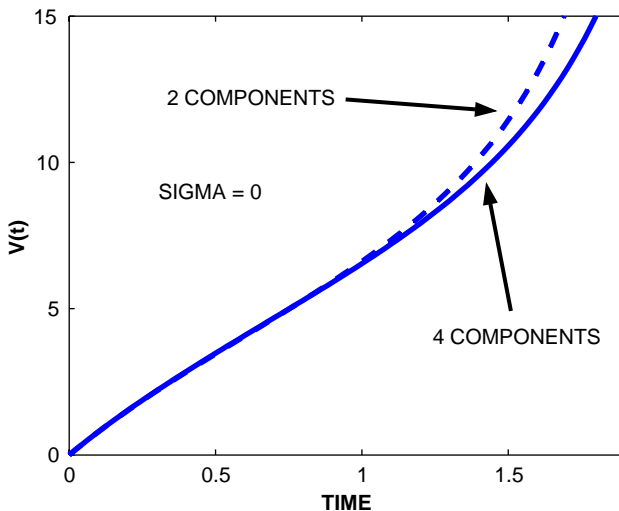


Fig. 1. Sample paths in the noise-free case for the 4-component model and the 2-component approximation.

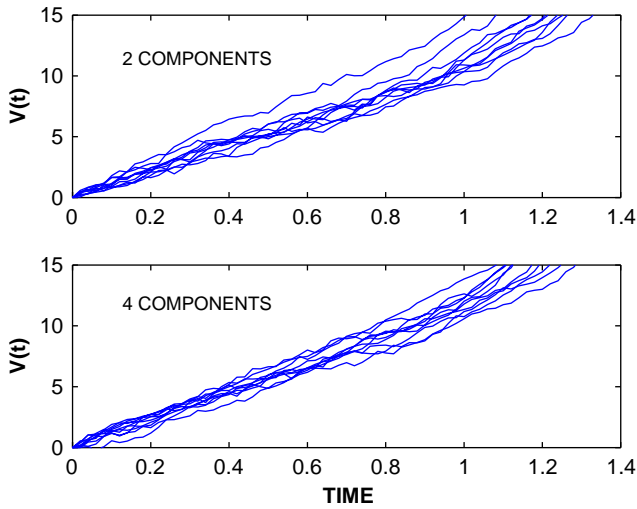


Fig. 2. Showing 10 subthreshold sample paths for the 2-component approximation and the 4-component model when $\mu = 15$ and $\sigma = 1.5$.

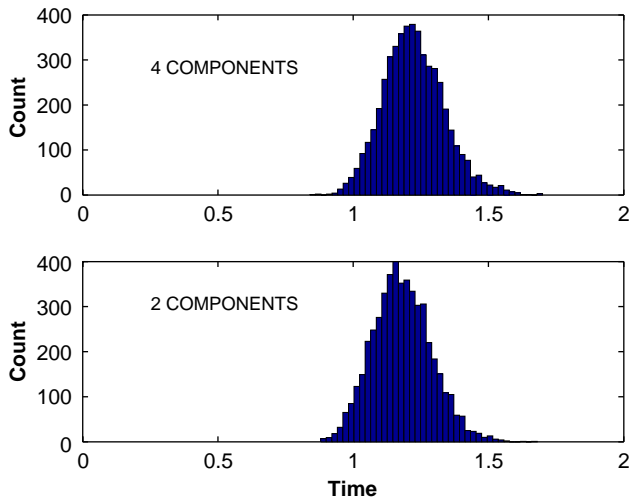


Fig. 3. Showing distributions (5000 trials) of time to reach threshold in the 2-component approximation and the 4-component Hodgkin–Huxley model when $\mu = 15$ and $\sigma = 1.5$.

3.1. Perturbation approach

For small values of σ , the PDE's for \bar{F} and \bar{G} are of the singular perturbation type. An outer asymptotic expansion of the exact solution can be obtained with a

parametric series in powers of σ^2 (we again drop bars on \hat{v} and \hat{y}):

$$\bar{F}(\hat{v}, \hat{y}; \sigma) \sim \sum_{n=0}^{\infty} F_n(\hat{v}, \hat{y})\sigma^{2n},$$

and similarly for \bar{G} . To solve the PDE's for \bar{F} and \bar{G} thus requires that the coefficients $\{F_n\}$ and $\{G_n\}$ be determined successively from a sequence of first-order linear PDE's which can be solved by the method of characteristics [19]. For example, the leading term solution $F_0(\hat{v}, \hat{y})$ for \bar{F} is determined by the following equation which is obtained simply by setting σ equal to zero in the above second-order PDE for \bar{F} :

$$P(\hat{v}, \hat{y}) \frac{\partial F_0}{\partial \hat{v}} + Q(\hat{v}, \hat{y}) \frac{\partial F_0}{\partial \hat{y}} = -1. \tag{8}$$

In this equation, the quantities P and Q are the coefficients of the first partial derivative terms with respect to \hat{v} and \hat{y} , respectively. Using a threshold value of $\bar{V} = v_\theta$, the value of F_0 at $\hat{v} = 0$ and $\hat{y} = m(0) = 0.06$ (standard value for the initial value of the sodium activation variable) is found by solving the corresponding characteristic ordinary equations (with \hat{y} and F_0 considered as functions of \hat{v})

$$\frac{d\hat{y}}{d\hat{v}} = \frac{Q(\hat{v}, \hat{y})}{P(\hat{v}, \hat{y})} \quad \text{and} \quad \frac{dF_0}{d\hat{v}} = -\frac{1}{P(\hat{v}, \hat{y})},$$

with the auxiliary conditions $\hat{y}(\hat{v} = 0) = y_0$ and $F_0(\hat{v} = v_\theta) = 0$. Using $F_0(\hat{v} = 0)$ as an approximate value for $\bar{F}(0, 0.06, \sigma)$ leads to an excellent approximation to the mean time to a spike for small σ , as obtained by simulation.

While of limited usefulness in some parameter ranges, the leading term perturbation solution for \bar{F} and \bar{G} gives accurate results for sufficiently large σ . This can be seen from a perturbation solution for these quantities in powers of $\frac{1}{\sigma^2}$

$$F^* = \exp\left[\frac{p(\hat{v}, \hat{y})}{\sigma^2}\right] \bar{F}(\hat{v}, \hat{y}; \sigma)$$

with

$$p(\hat{v}, \hat{y}) = \int^{\hat{v}} P(x, \hat{y}) dx = -\frac{\bar{a}_1}{2}(\hat{v} - \alpha)^2,$$

where we have re-grouped the coefficient of $\frac{\partial \bar{F}}{\partial \hat{v}}$ as a linear function of \hat{v} : $P(\hat{v}, \hat{y}) = \bar{a}_0 - \bar{a}_1 \hat{v}$, $\bar{a}_0 = \mu - k_1 + k_4 \hat{y}^3$, $\bar{a}_1 = k_2 + k_3 \hat{y}^3$ and $\alpha = \bar{a}_0 / \bar{a}_1$. Here we have defined the following constants $k_1 = -(\bar{g}_K n^4(0) V_K + g_I V_I)$, $k_2 = \bar{g}_K n^4(0) - g_I$, $k_3 = -\bar{g}_{Na} h(0)$ and $k_4 = \bar{g}_{Na} h(0) V_{Na}$. In terms of F^* the PDE for \bar{F} becomes

$$\frac{\sigma^2}{2} \frac{\partial^2 F^*}{\partial \hat{v}^2} - \frac{1}{2} \left(\frac{1}{\sigma^2} P^2 + \frac{\partial P}{\partial \hat{v}} \right) F^* + Q \frac{\partial F^*}{\partial \hat{y}} = -e^{p/\sigma^2}.$$

Note that F^* is a function of \hat{v} and \hat{y} with σ as a parameter. When σ is large, we seek a perturbation solution for $F(\hat{v}, \hat{y}; \sigma)$ in powers of σ^{-2} . For sufficiently large values of σ , the leading term F_0^* provides an adequate approximation to the solution. This

leading term satisfies the ordinary differential equation

$$\frac{\sigma^2 \partial^2 F_0^*}{2 \partial \hat{v}^2} = -e^{p/\sigma^2}, \tag{9}$$

that is, the equation for F^* with all terms on the left except the one multiplied by σ^2 omitted. The exact solution of this equation yields an approximation in terms of error functions:

$$F_0^*(\hat{v}, \hat{y}) = e^{p/\sigma^2} \overline{F}_0(\hat{v}, \hat{y}) = \int_{\hat{v}}^{\theta} g(\zeta) d\zeta,$$

where

$$\sqrt{\frac{\sigma^2 a_1}{2\pi}} g(\zeta) = 1 \pm \operatorname{erf}(\pm \tau(\zeta)),$$

for $\zeta > \alpha$, $\zeta < \alpha$, respectively, and where

$$\tau(x) = \sqrt{\frac{a_1}{2\sigma^2}}(x - \alpha).$$

Higher order correction terms in the perturbation solution may also be obtained with the solution of the previous step as forcing terms. Similar developments apply also to the equation for \overline{G} , but will not be pursued here for lack of space.

4. Results for the time to the first spike

Our calculations determine the moments of the first spike elicited from the rest in the presence of random synaptic input. These calculations could be extended to include a random initial state [30]. A systematic investigation was undertaken and we here give some representative results for the 2-dimensional analytic approach. The results, shown in the following table for $\sigma = 0$, obtained by exact solution of the first-order PDE (8) using the method of characteristics, indicate that this approach may give reasonable estimates of the time to firing (Table 1).

Table 1

	$E[\overline{T}_1]$	$E[\overline{T}_1]$	$E[T_1]$
μ	Calc.	Sim.	Sim.
5	3.757	3.76	4.47
10	1.676	1.68	1.79
15	1.137	1.14	1.19
20	0.866	0.87	0.89

Table 2

μ	$E[\bar{T}_1]$	$E[\bar{T}_1]$	$E[T_1]$
	Calc.	Sim.	Sim.
4	3.425	3.92	3.70
5	3.382	3.42	3.30
10	2.750	1.76	1.78

These results are also a good approximation for $\sigma \ll 1$ to those obtained by simulation of the 2-component process. Using the leading term approximation for the solution of Eq. (9), reasonable accuracy may be obtained for large values of σ as the following results for $\sigma = 10$ show (Table 2).

5. Discussion and conclusions

The problem of determining how often a neuron spikes in response to stochastic input processes has been the subject of numerous investigations using many simplified models [14]. In this article we considered using Markov process theory for the determination of the moments of the time to first spike in a random Hodgkin–Huxley model appealing to a 2-component approximation when the noise is relatively small. The time to first spike is an experimentally observed quantity in experiments involving sensory stimulation [3–7] and current injection [31]. The present model is relevant to such experimental observations because there is intrinsic additive noise due to random synaptic bombardment in cortical neurons [33], which may be approximated by a non-zero mean Gaussian white noise current. Allowance must be made for transmission times as outlined in Ref. [14], Chapter 10. For the first spike elicited from a rest state, one may accurately employ Markov process theory to, in principle, obtain all statistical properties, including moments and probability distribution. For the 2-component approximation we were able to formulate and solve approximately the partial differential equations for the moments of \bar{T}_1 , and found good or reasonable agreement with results from simulation of the stochastic differential equations. Such analytical calculations not only provide a useful check of simulation results but are of use, with appropriate allowance for cell biophysical and anatomical properties, in comparing experimentally observed first spike time statistics with theory. As an additionally useful result we were able to obtain the solution to the firing time problem in the case of no noise, thus effectively solving for the first time a difficult non-linear system of deterministic differential equations. There remains, however, the task of completely solving the PDE's (5) and (6) for the 4-component model, or related more complete models [26,27] by either analytical or accurate numerical methods.

Acknowledgements

HCT appreciates the hospitality of Professor Ruth J. Williams at UCSD Mathematics and Professor Juergen Jost at Max Planck Institute for MIS.

Appendix

Hodgkin–Huxley coefficients

$$\alpha_n(V) = \frac{10 - V}{100[e^{(10-V)/10} - 1]},$$

$$\beta_n(V) = \frac{1}{8} e^{-V/80},$$

$$\alpha_m(V) = \frac{25 - V}{10[e^{(25-V)/10} - 1]},$$

$$\beta_m(V) = 4e^{-V/18},$$

$$\alpha_h(V) = \frac{7}{100} e^{-V/20},$$

$$\beta_h(V) = \frac{1}{e^{(30-V)/10} + 1}.$$

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