Variability of Firing of Hodgkin-Huxley and FitzHugh-Nagumo Neurons with Stochastic Synaptic Input

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(Received 2 October 1998)

The variability and mean of the firing rate of Hodgkin-Huxley and FitzHugh-Nagumo neurons subjected to random synaptic input are only weakly dependent on the level of inhibitory input, unlike integrate-and-fire neurons. For the latter model, substantial inhibitory input is essential to ensure output variability close to Poissonian firing. It cannot therefore be used routinely in stochastic network modeling in place of biophysical models without first checking that the network behavior is not seriously compromised. [S0031-9007(99)09338-2]

PACS numbers: 87.19.La, 87.10.+e

All neurons fire irregularly when subjected to sufficiently low intensity Poissonian synaptic input, and almost all neurons fire regularly if driven very hard [1]. In between these two extremes, neurons vary in their response to stochastic input, although there has been little consensus in the literature about which key properties determine the nature of the response.

For example, there has been much discussion about the properties of leaky integrate-and-fire (IF) models in response to random synaptic input [2–5]. It has been claimed that—at realistic levels of random synaptic input—such neurons effectively integrate a large number of random inputs to produce an output which itself is of low variability [2,6,7] as measured by the coefficient of variation of the interspike interval [CV(ISI)]. However, other studies have shown the IF neuron to be capable of near-Poisson firing at realistic levels of excitatory input over a significant range of r, the ratio of the number of inhibitory to excitatory inputs [8–10]. For convenience, we here use the term "near-Poisson firing" as a shorthand for the occurrence of firing patterns with $0.5 < \mathrm{CV(ISI)} < 1$.

It has frequently been proposed [11,12] that, for network modeling purposes, IF neurons capture the essentials of the interneuronal behavior which more biophysically based models display. Of course, biophysical models act as threshold devices just like IF models, but some such models also show important differences in behavior. A first difference concerns the firing rate at different levels of constant applied current: Hodgkin [14] classified membranes as type I if they can show an arbitrarily low firing rate and long spike latency in response to a continuous current, or type II if they exhibit a narrow range of response firing rates (not close to zero) and virtually zero spike latency. A basic biophysical model—the Hodgkin-Huxley (HH) model of SQUID giant axon [13]—is classified as type II [15,16]. In a sense, the IF model can be classified as type I, since arbitrarily low firing rates are possible for just suprathreshold currents. Also, the HH model shows a complexity not shared with the IF model. When subjected to levels of constant continuous current which are close to the level required to induce continuous firing, it exhibits a bistability in which a stable rest state is coexistent with a continuously firing state [17,18].

The previous paragraph has discussed the responses of the neurons to constant current input, whereas in this paper our concern is with their response to random synaptic input. More specifically, we ask the question: Do biophysical models respond to random synaptic input in broadly the same manner as leaky integrator models? We consider as examples, well studied in other contexts, the HH model and a simplification often taken as the generic case of excitability, the FitzHugh-Nagumo (FHN) model [19,20]. We find that the IF model responds to synaptic input quite differently from the biophysical models, particularly in the relationship between the rate and variability of firing and the degree of balance between inhibition and excitation, r. For some levels of excitatory input, the HH and FHN models fire in the near-Poisson range independently of the value of r, whereas the spiking of the IF model becomes regular when $r \to 0$. We confirm these findings using a different model for excitatory postsynaptic potential/inhibitory postsynaptic potential (EPSP/IPSP) action and using different simulation software.

Many studies of single neurons and networks have been made using IF models, with a view to clarifying how information is encoded and transmitted in neuronal systems. Providing an answer to the question whether IF models provide an adequate simplification of biophysically based models is therefore important in the quest for a better understanding of the nature of the neural code.

Models and methods.—The HH model is

$$C\frac{dV}{dt} = I_{\mathrm{syn}} + g_K n^4 (V - V_K) + g_{N_a} m^3 h (V - V_{N_a}) + g_L (V - V_L), \quad (1)$$

where I_{syn} is the synaptic current. The model parameters and remaining three equations are as in [13]. The FHN model we used is a scaled version:

$$\frac{dV}{dt} = I_{\mathrm{syn}} + \gamma[-V(V - \alpha)(V - 1) - W], \quad (2)$$

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$$\frac{dW}{dt} = \delta[V - \beta W], \tag{3}$$

where $\alpha = 0.2$, $\beta = 2.5$, $\gamma = 100$, and $\delta = 0.25$. For comparison we simulate an IF model:

$$\frac{dV}{dt} = -\frac{V}{\gamma} + I_{\text{syn}}\,; \tag{4}$$

γ, the membrane decay time, equals 20.2 ms, a value appropriate for neurons in the visual cortex [21], although the exact value is not critical. In this model, when V reaches the threshold (20 mV above resting potential, taken here as zero), the neuron fires and V is reset to the resting potential.

I_{syn} is modeled as instantaneous perturbations of membrane potential. Thus, for the HH and IF model simulations, the effect of an EPSP/IPSP is an instantaneous perturbation of membrane potential of magnitude $a = 0.5$ mV. We confirmed that these results were not critically dependent on the specific value of a by also using a value of a of 2 mV. We also tried a different EPSP/IPSP model, in which the effect of an EPSP/IPSP is a square wave current of duration 0.1 ms of such a magnitude as to induce a change of 0.5 mV when close to the resting potential. Since the scaling of the FHN model was different, these were subject to EPSPs and IPSPs of the same frequency but of magnitude 0.06 to achieve mean firing rates within a similar range to the HH model.

The model neurons received input from N_E excitatory synapses, each following a Poisson process of rate λ_E, and N_I inhibitory synapses, each with Poisson rate λ_I. For all three models, simulations were carried out with $\lambda_E = \lambda_I = 100$ Hz with N_E varying between 25 and 200 (HH and FHN models) or 20 and 100 (IF model) and $r = N_I/N_E$ varying between 0 and 1.0 for each value of N_E.

Results.—For all models, very few or no spikes were obtained with the lowest numbers of excitatory synapses ($N_E = 25, 50$ for the HH and FHN models, and $N_E = 20$ for the IF model, except when $r = 0.1$ and 0.2, as discussed in the legend to Fig. 4 below). Therefore only those results for higher values of N_E, for which reliable statistics could be obtained, are presented in the remainder of this section.

Hodgkin-Huxley model: Mean ISI for $75 \leq N_E \leq 200$ varies between 17 and 110 ms (see Fig. 1B), all physiologically plausible values. For $N_E = 75$ and 100, CV(ISI) is approximately independent of r, taking values of about 0.8 and 0.7, respectively (Fig. 1A). For higher values of N_E, CV(ISI) is positively correlated with r, taking values as low as 0.1 for $N_E = 300$ and $r = 0$. This correlation can be accounted for by the effects of the neuron's refractory period, as we now show. When standard deviation of output ISI, s, is plotted against mean ISI, m, we obtain an approximate straight line with fitted equation,

$$s = 1.008(\pm 0.015)m - 12.26(\pm 0.77)\,, \tag{5}$$

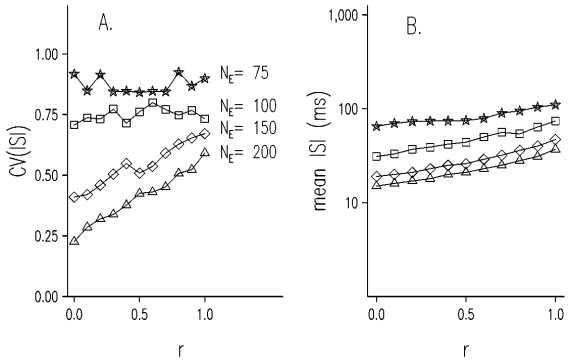

FIG. 1. Response of a HH neuron subject to N_E excitatory Poisson inputs, each of 100 Hz, and $N_I = rN_E$ inhibitory inputs with EPSP size = IPSP size = 0.5 mV. (A) CV(ISI) vs r for each value of N_E. (B) Mean ISI vs r for each value of N_E.

which intersects the m axis at about $12.26/1.008 = 12.2$ ms. This suggests an *effective* refractory period of about 12.2 ms (Fig. 2A). Standard errors of the fitted parameters (estimated by least squares) are given in brackets. The slope is not significantly different from one, consistent with the ISI following an exponential distribution with a displacement from zero of 12.2 ms. This means that, once the effective refractory period of 12.2 ms is subtracted from each interspike interval, CV(ISI) is approximately one, the expectation for Poissonian output. When adjusted values calculated on the assumption of such a displaced exponential distribution are plotted on the CV(ISI) vs r plot (Fig. 2B), a good fit is obtained, confirming that the output is consistent with Poissonian firing apart from the effects of the refractory period. This

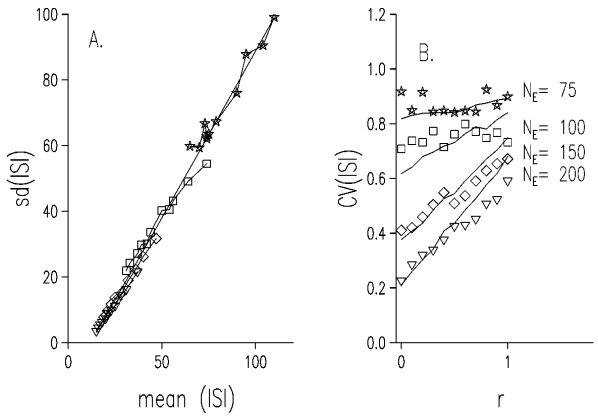

FIG. 2. Response of a HH neuron subject to N_E excitatory Poisson inputs, each of 100 Hz, and $N_I = rN_E$ inhibitory inputs with EPSP size = IPSP size = 0.5 mV. (A) s = s.d. (ISI) plotted against m = mean (ISI), and a fitted straight line, intersecting the x axis at about 12.2 ms. (B) CV(ISI) vs r with expected CV(ISI) calculated on the assumption that output follows a Poisson process, except for an initial refractory period estimated as 12.2 ms [i.e., predicted CV(ISI) = $(m - 12.2)/m$].

effective refractory period is similar to the period of the stable limit cycle (15–20 ms) which occurs in the absence of random synaptic input after a threshold continuous current is reached.

FitzHugh-Nagumo Model: For $75 \leq N_E \leq 200$, mean ISI varies between about 8 and 100 ms (Fig. 3B), comparable to the range obtained for the HH model at the same stimulation frequencies, and shows no strong relationship with r. CV(ISI) is also approximately independent of r for all values of N_E used in these simulations (Fig. 3A).

Comparison with integrate-and-fire model: The detailed properties of IF neurons in response to stochastic synaptic input have been described by the present authors elsewhere [8–10,22,23]. Mean ISI takes a very wide range of values as r is varied: from 6–15 ms when $r = 0.1$, depending on the value of N_E, to 1 s when $0.7 < r < 0.9$ for N_E taking values between 40 and 100 (Fig. 4B). By contrast, mean ISI for the HH and FHN models shows a much weaker correlation with r, of lower slope. A reduction in the strength of the inhibitory input therefore has a much greater impact on the firing rate of the IF neuron than the HH and FHN neurons. For $40 \leq N_E \leq 100$, CV(ISI) of the IF model is in the near-Poisson range for $r > 0.5$, falling substantially to near 0.25, as $r \rightarrow 0$ (Fig. 4A). For a significant range of values of r, CV(ISI) therefore takes values more typical of regular firing. This does not occur for the HH or for the FHN neuron. For the HH neuron, CV(ISI) is independent of r for $N_E = 75$ and 100, and for higher values of N_E, CV(ISI) only falls as a result of the neuron's refractory period. For the FHN neuron, CV(ISI) is high for all values of r at the stimulation frequencies used in our simulations.

Robustness of HH results; increasing EPSP size and different EPSP model: We simulated the HH model with a greater EPSP amplitude ($a = 2$ mV), to check that the results were not specific to a particular EPSP size. The results (not shown) were similar to those obtained for $a = 0.5$ mV, except that firing was attained at much lower EPSP rates (e.g., $N_E = 10$), as might be expected. Mean ISI ranges from slightly under 10 ms to about 40 ms, a lower and narrower range than for EPSPs of 0.5 mV, despite covering a wider range of N_E values in these simulations. The larger EPSP size clearly drives the neuron much faster, and hence we would expect that the effect of the refractory period of the neuron would be more pronounced. Nevertheless, for $N_E = 10$ and 25, CV(ISI) is independent of r, as for the smaller EPSP size, taking values of approximately 0.65 and 0.35, respectively. For higher numbers of inputs, CV(ISI) falls off as $r \rightarrow 0$, to values close to 0.2.

In order to check that the results were not dependent on the exact model used for EPSPs and IPSPs, we repeated the simulations on the package NEURON [24]. We modeled EPSPs and IPSPs as currents which had approximately the same effect at resting potential as an instantaneous voltage perturbation of 0.5 mV. The results (not presented) are very similar to those for the simpler form of EPSP (Fig. 1), except that CV(ISI) and mean ISI are lower for a fixed level of N_E. As before, for some values of N_E, CV(ISI) is independent of r, unlike the integrate-and-fire model.

Discussion.—The results show that the response of the HH and FHN models to stochastic synaptic input is rather different from that of IF models studied previously ([8–10,22,23]). For some intensities of stimulation, CV(ISI) of the HH and FHN models is independent of the degree of balance between excitation and inhibition, and consistent with near-Poisson behavior over the whole range of r between 0 and 1. For IF models, CV(ISI) is consistent with near-Poisson behavior only for higher values of r, falling to low values as $r \rightarrow 0$. The results for the IF model reported in this paper are consistent with our earlier results [8–10,22,23]. For higher intensities of stimulation, the refractory period of the HH neuron begins to exert its effect, and lower values of CV(ISI) occur. However, when the refractory period is adjusted for, firing

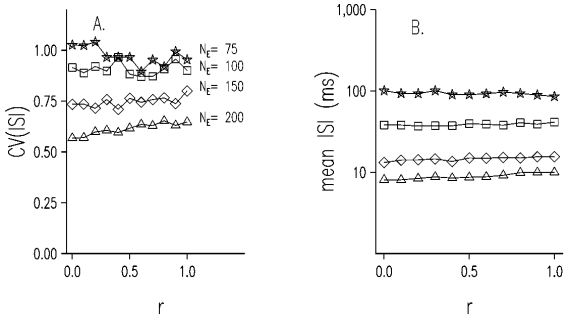

FIG. 3. Response of a FHN neuron subject to N_E excitatory Poisson inputs, each of 100 Hz, and $N_I = rN_E$ inhibitory inputs with EPSP size = IPSP size = 0.06 (in the scaled units of the FHN model). (A) CV(ISI) vs r for each value of N_E. (B) Mean ISI vs r for each value of N_E

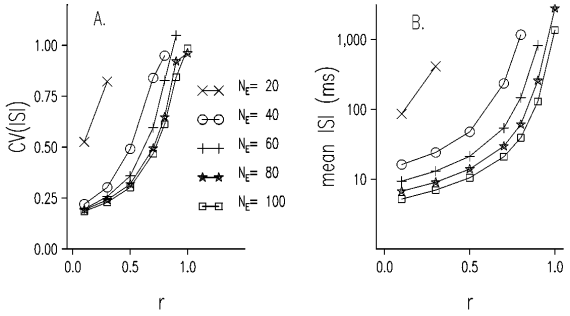

FIG. 4. Response of an IF neuron with $\gamma = 20.2$ ms subject to N_E excitatory Poisson inputs, each of 100 Hz, and $N_I = rN_E$ inhibitory inputs, where EPSP size = IPSP size = 0.5 mV. (A) CV(ISI) vs r for each value of N_E. (B) Mean ISI vs r. We also display here the results for $N_E = 20$, not discussed in the text, to demonstrate that, although higher values of mean and CV of ISI are obtained at lower levels of excitatory input, they still show a strong relationship with r.

again becomes consistent with a Poisson process. The mean ISI of the IF model decreases much more quickly as $r \to 0$ than for the HH and FHN models.

Biophysical models differ from IF models in a number of ways. They generally exhibit an absolute and relative refractory period. To reflect this, we could simply adjust the output of the IF model to include an absolute refractory period. However, that would further depress CV(ISI) for values of r close to zero even farther, and increase the disparity between the results for the IF and the HH and FHN neurons.

It was recently proposed that the nature of the membrane dynamics might be an important determinant of the response of neurons to random synaptic stimulation [25]. As described in the introduction, membranes were classified by Hodgkin [14] as of type I or type II, depending on their firing rate and current strength relationship. The HH and FHN models are both of type II [16,25]. Our results therefore do not agree with the predictions in [25], based on a study of the Morris-LeCar model, that type II neurons would display a low CV(ISI) in contrast to type I neurons with a high CV(ISI). Troyer and Miller [5] suggested that resetting the membrane potential after a spike to a level higher than the resting potential would promote more variable firing. This is not necessary for the HH model at moderate intensities of synaptic input. A number of authors [3,4] have asserted the need for exact balance in the inputs in order that $0.5 \leq \mathrm{CV(ISI)} \leq 1$, as observed in neurons in the visual cortex and elsewhere. The results in [10,22,23] demonstrate that substantial departures from exact balance could be tolerated with IF models while still preserving a $\mathrm{CV(ISI)} \geq 0.5$. The present study carries this a stage further in that, for the HH and FHN models, no inhibitory input is necessary at all at some input intensities in order that $\mathrm{CV(ISI)} \geq 0.5$. Whether this property will hold for other biophysical models is currently the subject of another study and will be reported elsewhere.

The present results, however, are sufficient to demonstrate that, when building network models, IF neurons cannot in general be substituted for biophysical models. For some parameter ranges their responses to random synaptic input are very different. This could be expected to have a substantial impact on the network behavior.

We are grateful to Andrew Davison for helpful comments on earlier versions of this manuscript. This work was financially supported by the BBSRC and the Royal Society.

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