LETTERS TO THE EDITOR

Dear Sir:

The random walk model for the quasi-stable interspike interval distribution presented in the recent paper by Gerstein and Mandelbrot (*Biophysic. J.*, 1964, **4**, 41) provides quite impressive agreement between theory and experiment despite a number of defects in the model discussed by the authors. Many neurophysiologists would have some additional reservations about the Gerstein-Mandelbrot model, the most serious of which is probably the following: the model assumes that the neuron's membrane potential is reset following each spike and, thus, that the random walk begins anew each time from the same point. In physiological terms this implies that the nerve impulse destroys all remaining postsynaptic potentials (PSP) or, in other words, that there is no transmitter persistence. On the other hand, it is assumed that each PSP moves the membrane potential one step either away from or toward the firing level and that the effect of the PSP persists essentially unchanged for the entire interspike interval. Since transmitter persistence is not allowed, such a long PSP would imply a membrane time constant of at least several hundreds of milliseconds (judging from the fact that there are appreciable numbers of intervals longer than 100 msec., see Figs. 5 and 6 by Gerstein and Mandelbrot). Time constants of this magnitude have not, of course, been observed in the cat nervous system.

Despite the inadequacies of the underlying physiological model, it would appear that the equation based upon this model (the diffusion equation) provides an adequate formal description of the rather characteristic long-tailed distributions obtained in some experiments (Fig. 5 and 6, Gerstein and Mandelbrot). This leads at once to the following question: might not the same equation also arise from alternative assumptions somewhat more acceptable to the neurophysiologist? The following derivation indicates that the diffusion equation can indeed be considered to be a formal description of neuron behavior frequently seen in intracellular recording experiments, and that it is consistent with a number of different physiological mechanisms.

It is well known that in intracellular records from several different types of repetitively discharging neurons, the membrane potential repolarizes at the end of each spike, and then increases approximately linearly to the firing level where the next spike is initiated. Superimposed upon this linearly increasing depolarization are haphazard membrane potential fluctuations; it would appear that these fluctuations, together with possible variations in firing level, are responsible for variability in interspike interval. The mechanism underlying the linear rise of membrane potential between spikes is not yet understood in detail, although presumably it involves slowly decreasing potassium conductance, increasing sodium conductance, and a voltage drop across the membrane resistance of synaptic or experimentally applied current. Nor are the sources of superimposed membrane potential fluctuations known: thermal noise, synaptic "noise" analogous to the spontaneous miniature end-plate potentials of the muscle end-plate, random synaptic bombardment of the type assumed in the Gerstein-Mandelbrot model, and variability inherent in the membrane conductance changes are all possibilities, and the evaluation of their relative contributions awaits experimental investigation.

Without specifying the exact sources of superimposed membrane potential fluctua-

tions, the following equation represents a formal description of the process outlined in the preceding paragraph:

$$x(t) = \beta - \alpha t + F(t) + M(t); \qquad t \geq 0 \tag{1}$$

Here, $x(t)$ is the distance (in millivolts) of the membrane potential from the firing level, t is the time since the last spike, α is the rate of depolarization between spikes, β is the distance from the firing level immediately after a spike has occurred, and $F(t)$ and $M(t)$ are appropriate random functions representing variations in firing level and membrane potential fluctuations, respectively. Although all of the sources of membrane potential fluctuation have been lumped into the single function $M(t)$, it would have been possible to include each of these separately without changing the form of the final equation; this will become apparent in the following derivation.

The preceding equation is as yet an incomplete description since it is necessary to place restrictions upon the random functions $M(t)$ and $F(t)$. We shall suppose them to be Gaussian, stationary, independent of $x(t)$ and of each other and further, to have zero means and correlation functions of the form e^{-mt} and e^{-ft}, respectively. These restrictions are mathematically convenient and at the same time realistic in the sense that their justification is possible for any of the noise sources enumerated earlier. For example, random membrane potential fluctuations from any source might be expected to have an approximately exponential correlation function simply because of the neuron's resistance-capacitance (RC) properties (white noise through a parallel RC circuit has this correlation function).

It can be shown that for a (Markov) system such as we have described, the probability $p(x, t)$ that the membrane potential is x millivolts away from the firing level at time t is given by the Fokker-Planck (or Kolmogorov forward) equation:

$$\frac{\partial p}{\partial t} = \frac{\partial}{\partial x}(pA(x)) + \frac{1}{2}\frac{\partial^2}{\partial x^2}(pB(x))$$

(A readable discussion of this equation may be found in Chapter X of Gnedenko, B. V., The Theory of Probability, (B. D. Seckler, translator), New York, Chelsea Publishing Company, 1962; or Wang, M. C., and Uhlenbeck, G. E., On the Theory of Browian Motion II, *in* Noise and Stochastic Processes, (N. Wax, editor), New York, Dover Publications, Inc., 1954.) The functions $A(x)$ and $B(x)$ are determined from equation (1) and the properties of the random functions $M(t)$ and $F(t)$, and can be shown for our case to be:

$$A(x) = -\alpha, \qquad B(x) = 2(f + m)$$

Substitution of these values into the Fokker-Planck equation yields the equation of Gerstein and Mandelbrot (p. 52) except that they have chosen units to make $(f + m)$ equal to unity; this maneuver does not affect the form of the first passage time distribution calculated from the diffusion equation, and it is this distribution which is compared with experimental observations.

Thus, any source (or combination of sources) of noise with approximately the properties specified above would give rise to the equation presented by Gerstein and Mandelbrot. It should be emphasized that this equation could have been derived as an approximate description of neuron behavior under weaker restrictions than those imposed above, but such a derivation would entail a lengthy discussion. The decision as to whether the particular type of neuron discussed by Gerstein and Mandelbrot, or indeed any neuron

at all, behaves according to the above description must, of course, await intracellular recording experiments. Since the diffusion equation appears to be an almost inevitable result for many noise sources, detailed investigations will be necessary to discover the exact physiological mechanism underlying the observed interspike interval distributions, even if the above equation proves to be accurate. Certainly, until such experiments are available, guesses about the mechanism would appear to be quite hazardous.

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CHARLES F. STEVENS
Department of Physiology and Biophysics
University of Washington
School of Medicine
Seattle, Washington