

Synaptic Transmission in a Model for Stochastic Neural Activity

HENRY C. TUCKWELL

*Department of Mathematics, University of British Columbia,
Vancouver, B.C., Canada*

(Received 20 October 1977, and in revised form 10 August 1978)

A stochastic model equation for nerve membrane depolarization is derived which incorporates properties of synaptic transmission with a Rall–Eccles circuit for a trigger zone. If input processes are Poisson the depolarization is a Markov process for which equations for the moments of the interspike interval can be written down. An analytic result for the mean interval is obtained in a special case. The effect of the excitatory reversal potential is considerable if it is not too far from threshold and if the interspike interval is long. Computer simulations were performed when inhibitory and excitatory inputs are active. A substantial amount of inhibition leads to an exceedingly long tail in the density of the interspike time. With excitation only the interspike interval is often an approximately lognormal random variable. A coefficient of variation greater than one is often a consequence of relatively strong inhibition. Inferences can be made on the nature of the synaptic input from the statistics and density of the time between spikes. The inhibitory reversal potential usually has a relatively small effect except when the frequency of inhibition is large. An appendix contains the model equations in the case of an arbitrary distribution of postsynaptic potential amplitudes.

1. Introduction

Various models have been employed for determining the responses of neurons to random synaptic input. A comprehensive review has been compiled by Holden (1976) and some additional references can be found in Yang & Chen (1978). Each kind of neuron and its input processes have special features which need to be taken into account when modelling its spiking activity to any degree of accuracy. Usually, many important electrophysiological properties of neurons and in particular the details of the nature of synaptic transmission are omitted in the formulation of the models.

Thus far in the theoretical studies of neuronal response to random input, the emphasis has been on “point” models. That is, the spatial extent of the neuronal surface is ignored and the quantity studied is taken to have a single

component. We are currently working on spatial models (Wan & Tuckwell, 1979), but for them the first passage problem is much more difficult. Stein (1965) first included the exponential decay of nerve membrane potential towards its resting value when no synaptic inputs were active. Stein's model, which has amplitudes of excitatory and inhibitory postsynaptic potentials of fixed magnitudes, contains an oversimplification of the generation of these potentials. An attempt will be made here to improve Stein's model by including a more realistic description of synaptic transmission whilst at the same time retaining the model's simplifying features.

It is useful to introduce some notations for random processes which make the presentation of various models particularly transparent. The symbol $P(f; t)$ will denote the value of a temporally homogeneous Poisson process of rate parameter f at time t , assuming $P(f; t = 0) = 0$. Thus, the probability that this process takes on the value k at time t is given by

$$\Pr (P(f; t) = k) = \frac{(ft)^k e^{-ft}}{k!}. \quad (1)$$

The increment in such a process in an infinitesimal time interval is denoted by $dP(f; t)$. A standard (zero mean, variance = t) Brownian motion or Wiener process will be denoted by $W(t)$. Hence, if $W(0) = 0$,

$$\Pr (x < W(t) \leq x + dx) = \frac{dx}{(2\pi t)^{\frac{1}{2}}} \exp(-x^2/2t), \quad (2)$$

and an infinitesimal increment of $W(t)$ is denoted by $dW(t)$.

In Stein's model an R-C circuit represents a patch of nerve membrane. If excitation arrives with rate f_E and generates an excitatory postsynaptic potential (epsp) of amplitude E and inhibition arrives at rate f_I with an inhibitory postsynaptic potential (ipsp) of amplitude I , then the depolarization $V(t)$ at the trigger zone satisfies the stochastic differential equation

$$dV(t) = -sV(t) dt + E dP(f_E; t) - I dP(f_I; t), \quad V(0) = 0, \quad (3)$$

where $s = (RC)^{-1}$ is the reciprocal of the time constant, t . An unrealistic feature of this model is that the magnitudes of the changes in $V(t)$, which occur when events occur in the Poisson processes, are independent of $V(t)$. Furthermore, as pointed out in a previous note (Tuckwell, 1977), the depolarization satisfying equation (3) or its diffusion approximation $V^*(t)$, which satisfies

$$dV^*(t) = (-sV^*(t) + f_E E - f_I I) dt + (f_E E^2 + f_I I^2)^{\frac{1}{2}} dW(t), \quad (4)$$

can wander off to very large negative values (extreme hyperpolarizations)

which is not the case for real neurons. If one tries to overcome this difficulty by asking not for the time that the depolarization first leaves the interval $(-\infty, \theta)$, where θ is the threshold depolarization for action potential generation, but rather the first time at which V or V^* leaves the interval $(-\theta_1, \theta)$, then one is confronted with exits at $-\theta_1$ which do not produce spikes. Though one may try to overcome this problem by asking for the exit time conditioned on escape at θ , the relation between this conditioned random variable and the actual time between spikes is not able to be directly ascertained. As will be seen in the next section, when the nature of the generation of postsynaptic potentials is included in the model, this complication disappears and the responses of the neuron correctly depend on the depolarization present when the input stimulus arrives.

2. Inclusion of the Nature of Synaptic Transmission

A great deal has been learned about synaptic transmission in the last few decades [see, for example, Krnjevic (1974)], though the picture is far from complete. It is usually understood that arriving action potentials in presynaptic terminals cause a release of transmitter substance which thereupon leads to conductance changes in postsynaptic membrane. Various transmitters lead to different kinds of conductance changes and the latter depends on the nature of the receptors on the postsynaptic membrane as well as on the transmitter substance. Acetylcholine is an excitatory transmitter at motoneuron-Renshaw cell synapses and increases in conductance of both Na^+ and K^+ are believed to occur. Glycine is suspected to be the inhibitory transmitter at Renshaw cell-motoneuron synapses and a chloride conductance change is supposed to occur. The putative transmitter L-glutamate exerts an excitatory effect by increasing Na^+ conductance and to a lesser extent K^+ conductance.

Despite the non-uniqueness of the action of a given transmitter, at a given synaptic junction the transmitter action can be characterized by a reversal potential. This is the membrane potential at which the observed potential change due to the transmitter induced conductance change is zero. For example, a recurrent ipsp mediated by glycine occurs when Renshaw cells spike and the motoneuronal membrane potential is at its resting value. If a hyperpolarizing current is injected into the motoneuron to hold its membrane potential a few mV below its resting value, no ipsp is seen, and further hyperpolarization leads to a response which appears as an epsp (Burke, Fedina & Lundberg (1971)). The effect of the glycine induced conductance change is to drive the membrane towards the chloride equilibrium potential. If a transmitter causes increases in both Na^+ and K^+

conductances, then the membrane potential is driven to a value between the equilibrium potentials for Na^+ and K^+ .

Reversal potentials have been taken into account in deterministic modelling of neuronal membrane when circuit diagrams were given with "batteries" for epsp and ipsp generation (Eccles, 1957; Rall, 1964). The same principle was employed in models for studying subthreshold and suprathreshold potential trajectories in axons (Hodgkin & Huxley, 1952). We assume here that the neuron has excitatory synapses which when activated result in a driving of $V(t)$ towards the reversal potential V_E , whereas inhibition drives $V(t)$ towards V_I , with $V_E > 0$ and $V_I < 0$. It is assumed that the internal and external ion concentrations do not change significantly so that V_E and V_I can be regarded as constants. The associated conductances, which are random processes and may have contributions from more than one ion type, are denoted by g_E and g_I and the "passive" or non-synaptic membrane conductance is denoted g_R .

Let the number of excitatory and inhibitory synaptic events up to time t be $P_E(t)$ and $P_I(t)$ respectively. These random processes can take on only non-negative integer values. Let a single one of these events cause a release of transmitter of amount either Q_E or Q_I , assumed to be fixed (see the Appendix for the general case). The total amounts of transmitter released up to time t are thus $Q_E P_E(t)$ and $Q_I P_I(t)$. Transmitter is often only effective in producing a conductance change for a short time interval, denoted by ΔT_E or ΔT_I . This short lasting effect is due to several mechanisms amongst which may be glial uptake, presynaptic terminal uptake, removal by chemical decomposition (for example by hydrolysis in the presence of acetylcholine-esterase in the case of acetylcholine) or by diffusion away from receptors. The *effective* amounts of transmitter at time t are thus

$$Q_E(P_E(t) - P_E(t - \Delta T_E)) \quad \text{and} \quad Q_I(P_I(t) - P_I(t - \Delta T_I)).$$

We assume that $g_E(t)$ and $g_I(t)$ are proportional to the effective amounts of transmitter, with unit amounts producing conductance changes Δg_E and Δg_I . The stochastic differential equation for the depolarization is thus

$$C \frac{dV}{dt} = -g_R V + (V_E - V)Q_E \Delta g_E (P_E(t) - P_E(t - \Delta T_E)) \\ + (V_I - V)Q_I \Delta g_I (P_I(t) - P_I(t - \Delta T_I)). \quad (5)$$

Note that $V(t)$ here is not a Markov process no matter what kind of point processes $P_E(t)$ and $P_I(t)$ are assumed to be. We now utilize the fact that ΔT_E and ΔT_I are small whereupon

$$P_E(t - \Delta T_E) \simeq P_E(t) - \Delta T_E \frac{dP_E(t)}{dt} \quad (6)$$

$$P_I(t - \Delta T_I) \simeq P_I(t) - \Delta T_I \frac{dP_I(t)}{dt}. \quad (7)$$

To a good approximation the stochastic differential equation for V is

$$\frac{dV}{dt} = -sV + (V_E - V)a_E \frac{dP_E}{dt} + (V_I - V)a_I \frac{dP_I}{dt}, \quad (8)$$

where $a_E = Q_E \Delta g_E \Delta T_E / C$, $a_I = Q_I \Delta g_I \Delta T_I / C$ and $s = g_R / C$. The derivatives of the processes P_E and P_I are random time sequences of delta functions. The solution $V(t)$ of (8) is not necessarily a Markov process except in the case where P_E and P_I are independent-increment processes (i.e. Poisson processes). We then have

$$dV = -sV dt + (V_E - V)a_E dP(f_E; t) + (V_I - V)a_I dP(f_I; t), \quad (9)$$

which can be compared with equation (3). Though the assumption that $P_E(t)$ and $P_I(t)$ are Poisson may not always be realistic, the first passage time theory is presently only available for Markov processes, so we shall in the rest of this article concentrate on equation (9) rather than the more general model of equation (8).

3. Analysis of the Model and Analytic Results for a Special Case

The solution of (9) can be formally written

$$V(t) = V(0) - s \int_0^t V(t') dt' + a_E \int_0^t (V_E - V(t')) dP(f_E; t') \\ + a_I \int_0^t (V_I - V(t')) dP(f_I; t'), \quad (10)$$

where the stochastic integrals are defined as in Skorohod (1965). If $V(0) = 0$ and there are no barriers, then $V(t)$ would be constrained to move between V_I and V_E . The values V_E and V_I are inaccessible to $V(t)$ because the closer $V(t)$ gets to them the smaller are the epsp and ipsp amplitudes. To study nerve firing a threshold depolarization θ is introduced such that $V_I < V(0) < \theta < V_E$. The time between action potentials is the time at which $V(t)$ first reaches or exceeds θ . This is also the time at which $V(t)$ first exits from the interval (V_I, θ) if inhibitory inputs are active. $V(t)$ cannot wander off to extremely hyperpolarized states and furthermore there is no need to take account of exits at V_I because these cannot occur. Note that V_I is not a reflecting barrier of the kind introduced by Johannesma (1968) who considered a diffusion analog of equation (9). Note, too, that if there are no inhibitory inputs then 0 is an inaccessible value for $V(t)$ after the first epsp has occurred.

Suppose now that $p(v, t, x, t_1)$ is the transition probability density function of $V(t)$ when this process is not restricted by any barriers. From Gihman &

Skorohod (1972) this transition density satisfies the backward Kolmogorov equation

$$-\frac{\partial p}{\partial t_1} = -(f_E + f_I)p - s x \frac{\partial p}{\partial x} + f_E p(x + (V_E - x)a_E) + f_I p(x + (V_I - x)a_I), \quad (11)$$

with natural boundary conditions.

The expectation of $V(t)$ can be found from the forward Kolmogorov equation:

$$\frac{\partial p}{\partial t} = \frac{\partial}{\partial v} (s v p) + f_E p(v - (V_E - v)a_E) + f_I p(v - (V_I - v)a_I) - (f_E + f_I)p. \quad (12)$$

If we multiply throughout by v and integrate from $v = V_I$ to V_E we obtain an ordinary differential equation for the mean depolarization $\hat{V}(t)$:

$$d\hat{V}/dt = \hat{V}[-s + f_E((1 + a_E)^{-2} - 1) + f_I((1 + a_I)^{-2} - 1)] + V_E a_E f_E (1 + a_E)^{-2} + V_I a_I f_I (1 + a_I)^{-2}. \quad (13)$$

If we let the coefficient of $-V$ here be s' and the constant terms be k , the solution of this equation with $V(0) = 0$ is

$$\hat{V}(t) = k(1 - \exp(-s't))/s', \quad (14)$$

with asymptotic value $\hat{V}(\infty) = k/s'$. It is clear that if $\hat{V}(\infty) < \theta$, then the expected time between nerve impulses will be exceedingly long and the cell will be effectively inactive. Furthermore, in the case $\hat{V}(\infty) \geq \theta$, an approximate estimate of the mean interspike time is

$$T = T_R + (1/s') \ln [k/(k - \theta s')], \quad (15)$$

where T_R is the absolute refractory period and it is again assumed that $V(0) = 0$. This expression is derived simply by setting $\hat{V}(T) = \theta$, as was done by Stein (1965) and Roy & Smith (1969).

To obtain a more precise estimate of the interspike time it is necessary to consider the first passage time of $V(t)$ to θ . If $T_\theta(x)$ is the first time that $V(t)$ leaves the interval (V_I, θ) , so causing the generation of an action potential, then the expectation of $T_\theta(x)$, denoted by $F(x)$, satisfies the differential-difference equation

$$L[F(x)] = -(f_E + f_I)F(x) - s x \frac{dF}{dx} + f_E F(x + (V_E - x)a_E) + f_I F(x + (V_I - x)a_I) = -1, \quad (16)$$

which defines the operator L . Here x is the initial depolarization, and the equation is valid for $V_I < x < \theta$, with boundary condition $F(x) = 0$ for

$x \notin (V_I, \theta)$ and the further condition that $F(x)$ is continuous and bounded on (V_I, θ) . Note that $F(x)$ must be a monotonically decreasing function of x as x goes from V_I to θ . If $P^*(x)$ is the probability that $V(t)$ leaves the interval (V_I, θ) , then

$$L[P^*(x)] = 0, \quad V_I < x < \theta, \tag{17}$$

with $P^*(x) = 1$ for $x \notin (V_I, \theta)$. It is apparent that $P^*(x) = 1$ is a solution of equation (17) so that we conclude $T_\theta(x)$ has finite moments. If $M_n(x)$ is the n th moment, we have the recursion formulae (Tuckwell, 1976)

$$L[M_n(x)] = -nM_{n-1}, \quad n = 0, 1, 2, \dots \tag{18}$$

with $M_0 = P^*$ and $M_1 = F$. The conditions for (18) are the same as for (16).

(A) ANALYTIC SOLUTION FOR A SPECIAL CASE

Analytic solutions for the expected interspike time, $F(0)$, seem only able to be found in the cases of no inhibitory input and small ratios of the threshold to epsp amplitude, elicited from resting level. It is useful, nevertheless, to have such analytic solutions for a comparison with numerical solutions and to test the accuracy of computer simulations. A solution will be obtained for equation (16) when $f_I = 0$ and $f_E = s$.

Unlike the corresponding equation for Stein's model, the length of the subintervals on which equation (16) becomes an ordinary differential equation, when the solution is known on the next subinterval, are not of equal lengths. We will find that value of θ which gives rise to two subintervals between 0 and θ . For convenience set $G(x) = f_E F(x)$ so that

$$-x \, dG/dx + G(x + (V_E - x)a_E) - G(x) = -1, \quad x \in (0, \theta). \tag{19}$$

Let $\theta_1 = (\theta - V_E a_E)/(1 - a_E)$. Then $G(x + (V_E - x)a_E)$ vanishes due to the boundary condition if $x > \theta_1$. On the subinterval (θ_1, θ) , we then have

$$dG_1/dx + (G_1/x) = 1/x, \tag{20}$$

with solution

$$G_1(x) = 1 + (c_1/x), \tag{21}$$

where c_1 is a constant of integration. When $x + (V_E - x)a_E > \theta_1$, the second term in (19) is now known, and since we require the second subinterval to be $(0, \theta_1)$ we find $\theta = V_E a_E(2 - a_E)$. On $(0, \theta_1)$, we have

$$dG_2/dx + (G_2/x) = (2 + c_1/(x + (V_E - x)a_E))/x, \tag{22}$$

with solution

$$G_2(x) = 2 + \frac{1}{x} \left[\frac{c_1}{1 - a_E} \ln \{x(1 - a_E) + V_E a_E\} + c_2 \right]. \tag{23}$$

As $x \rightarrow 0^+$ we require $G_2(x)$ to be bounded and this leads to

$$\frac{c_1}{(1-a_E)} \ln(V_E a_E) + c_2 = 0. \quad (24)$$

Continuity requires $G_2(\theta_1^+) = G_1(\theta_1^-)$ which gives a second relation between c_1 and the second integration constant c_2 .

The expectation of the time at which the depolarization first reaches or exceeds 0 is thus (ignoring refractoriness)

$$E[T_\theta(0)] = \frac{1}{f_E} \left[2 + \frac{c_1}{V_E a_E} \right], \quad (25)$$

where

$$c_1 = \frac{\theta - V_E a_E}{1 - a_E + \ln(V_E a_E / \theta)}. \quad (26)$$

Though this result is obtained in a special case, we may use it to indicate how important neglect of the excitatory reversal potential will be in the calculation of the interspike time. To do this we can compare the above calculated value with that for Stein's model with $\theta = 1 + \theta^*$, $0 < \theta^* \leq 1$ (Tuckwell, 1976):

$$E[T_\theta(0)] = \frac{1}{f_E} \left[2 + \frac{\theta^*}{1 - \ln(1 + \theta^*)} \right]. \quad (27)$$

When $V_E = 50$, $a_E = 0.02$, so that $\theta = 1.98$, the mean interspike intervals are 5.3007 and 5.0924 time constants when the reversal potential is included and for Stein's model, respectively. The difference here is only 3.9% due to the fact that the reversal potential is a long way from θ and has little effect on the epsp amplitudes. When, however, the threshold is not far from the reversal potential, the differences become quite large. Thus, if $V_E = 5$, $a_E = 0.2$, giving $\theta = 1.9$ (i.e. about two-fifths of the excitatory reversal potential which is not physiologically unreasonable), equation (25) gives an expected time to firing of 5.7698 whereas Stein's model gives 3.9407. The difference here is 31.7%. Thus the inclusion of the excitatory reversal potential can be important, especially when θ is a significantly large fraction of V_E .

For a given θ , f_E and τ there are two factors which determine the firing rate. One is the ratio of the threshold to epsp amplitude elicited at rest, the other is the ratio of the threshold to V_E . The largest epsp amplitude (in the absence of inhibition) is $a_E V_E = \varepsilon_{\max}$, and this is the constant amplitude if V_E is ignored. The smallest possible subthreshold epsp is of amplitude $a_E(V_E - \theta) = \varepsilon_{\min}$. The ratio of threshold to epsp amplitude is a measure of the "height" of the threshold and the mean interspike interval has an approximately exponential

dependence on this quantity (Tuckwell & Richter, 1978). This ratio has a minimum value $\rho_{\min} = \theta/\varepsilon_{\max}$ and a maximum value $\rho_{\max} = \theta/\varepsilon_{\min}$. It is clear that when the excitatory reversal potential is included the interspike interval is bounded below by the interval for Stein's model with threshold to epsp amplitude ratio equal to ρ_{\min} and bounded above by the interspike interval with threshold to epsp amplitude ratio equal to ρ_{\max} .

4. Computer Simulations

Since analytic solutions for neither the interspike interval density nor its moments could be found in general, computer simulations were performed for the depolarization satisfying equation (9). So that a comparison with Stein's model can be made it is convenient to introduce the stochastic equation

$$dV = -sV dt + (V_E - \alpha V)a_E dP(f_E; t) + (V_I - \beta V)a_I dP(f_I; t). \quad (28)$$

If $\alpha = \beta = 0$ we obtain Stein's model in which excitatory and inhibitory reversal potentials are ignored. If $\alpha = 0$ and $\beta = 1$ we are ignoring the excitatory reversal potential but not the inhibitory one.

In the simulations the values of θ were chosen to be quite small relative to the amplitudes of the postsynaptic potentials in order to obtain physiological mean interspike intervals at moderate input frequencies. This enabled sufficient trials to be run to make the sampling errors sufficiently small. Small values of the ratio of θ to postsynaptic potential amplitudes to occur in some neurons, especially in the case of excitation [e.g. in anterior ventral cochlear nucleus cells of *cat* (Molnar & Pfeiffer, 1968) and cells of Clarke's column (Eide, Fedina, Jansen, Lundberg & Vyklicky, 1969; Jansen, Nicolaysen & Rudjord, 1966)]. In all the simulations we have set the time constant of decay at 5.8 ms which is the value for cat spinal motoneurons (Jack, Miller, Porter & Redman, 1971).

(A) GENERAL EFFECTS OF INHIBITORY INPUTS

Figure 1 shows interspike interval histograms for excitation only and for excitation together with inhibition at one-half the frequency of excitation. Approximating curves were drawn through the bin counts, the bin widths being one-half a millisecond. The refractory period has been ignored. Values of the parameters for this run are: $\theta = 10$ mV, $V_E = 100$ mV, $V_I = -10$ mV, $a_E = 0.02$, $a_I = 0.2$ (making both the epsp and ipsp amplitudes 1 mV at rest), $\tau = 1/s = 5.8$ ms, $V(0) = 0$, $\alpha = \beta = 1$ (both reversal potentials included). In the run with excitation only, $f_E = 8s \approx 1400 s^{-1}$, and in the run with

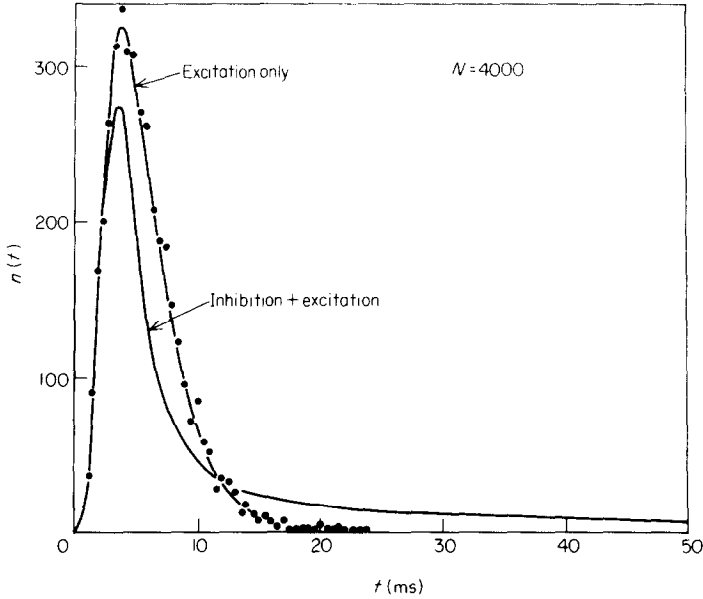


FIG. 1. Interspike interval densities obtained from computer simulations for the model equation (9) for excitation only and for excitation with inhibition at half the frequency of excitation. Parameter values given in text. The curves are visual best fits through bin counts which are shown for the case of excitation only.

excitation and inhibition, $f_E = 8$ s and $f_I = 4$ s. Each histogram is based on 4000 simulated action potentials. To check the reliability of the simulation procedures a control run was done with $\alpha = 0$ (no excitatory reversal potential) and $f_E = 8$ s in the absence of inhibition. The moments were in excellent agreement with the calculated moments (Tuckwell & Richter, 1978). The following data and observations emerge from the simulations.

- (i) Both histograms are unimodal.
- (ii) The initial slopes of the histograms are about the same.
- (iii) The histogram in the case with inhibition has a narrower and somewhat smaller peak. Its most noticeable feature is its extremely long tail. One interspike time was 183 ms, whereas with excitation only the largest interspike time was 24 ms.
- (iv) The modes are practically the same (about 4 ms) in both cases.
- (v) The medians are not very different: 5 ms for excitation only and 6.2 ms when inhibition is present.
- (vi) First, second and third moments, in ms, ms^2 and ms^3 are 5.83, 43.9, 414 for excitation only, 14.6, 562 and 36,110 for excitation with inhibition. The progressively disproportionate increase in the second and third

moments in the second case is due to the exceedingly long tail. The coefficients of variation are 0.54 for excitation only and 1.27 for excitation with inhibition, the corresponding skews being 0.69 and 1.36.

(vii) The output frequency (reciprocal of the mean interspike time) is approximately halved with inhibition half as strong as excitation. This is in agreement with an analytic treatment of an approximation to Stein's model (Tuckwell, 1975).

Burns & Webb (1976) have plotted histograms of interspike times for many cat cerebral cortical cells in different anatomical locations and whilst the animals were in various behavioural states. A class of cells was found whose interspike time was approximately a lognormal random variable. Another class of cells, which were more slowly firing, had interspike times which were about lognormal except that there was an excess of long intervals. The data of Fig. 1 was plotted with time logarithmically and the interspike time for excitation only was approximately lognormal whereas the density with inhibition was approximately lognormal except for an excess of long intervals. As pointed out (Tuckwell, 1978) it seemed plausible that the results for the simulations could provide a basis for the experimental results of Burns & Webb (1976). It seems, however, that a sharp classification should be replaced by more of a continuum of cell types. A cell receiving mostly excitation and small amounts of inhibition should have an interspike time which is approximately lognormal. The tail should gradually become more pronounced as the relative strength of the inhibition grows. It is pointed out that some of the results we have noted with inhibition have been indicated previously (Goel, Richter-Dyn & Clay, 1972).

(B) EFFECTS OF INCREASING INHIBITION WITH FIXED EXCITATION

If the postsynaptic potential amplitudes, threshold, time constant and reversal potentials are fixed, then the time between action potentials is a function (random) of the two input frequencies f_E and f_I . It is of interest to see how the output frequency depends on f_E for fixed f_I and on f_I at fixed f_E . A comprehensive study by computer simulation is not practicable but we have studied a few simple cases. Some progress has recently been made in calculating the mean interspike time for Stein's model with excitation and inhibition (Cope & Tuckwell, 1979).

Simulations reported here have the following parameter values: $s = (0.0058 \text{ s})^{-1}$, $V_E = 90 \text{ mV}$, $V_I = -9 \text{ mV}$, $\theta = 9 \text{ mV}$, $a_E = 1/30$, $a_I = 1/3$, so that psp amplitudes are 3 mV at rest. The reversal potentials are included so that $\alpha = \beta = 1$. Three excitation frequencies were used: $f_E = s$, $2s$ and $3s$ (172, 345 and 517 s^{-1}). In each case the frequencies of inhibition were $f_I = 0$,

0.2s, 0.4s, 0.6s, 0.8s and s. The shapes of the histograms with excitation only were as reported in the last subsection and the effect of increasing inhibition was to shift interspike time density to produce a long tail.

Figure 2 shows the mean output frequency f as functions of f_I at the three values of f_E . For $f_E = 2s$ and $f_E = 3s$, two curves are drawn, the lower ones taking into account an absolute refractory period of 1.5 ms. When $f_E = s$ the two curves are indistinguishable. The decline in f for $f_E = s$ is nearly linear in f_I . For the higher f_E values the decline in f seems more gentle initially and then becomes linear at higher f_I . Some caution is needed in accepting the results for small interspike times because only a few random numbers are used in their generation. It is clear, however, that the "net excitation", defined as $E = f_E a_E V_E + f_I a_I V_I$, is not a good measure of the state of activity of the neuron. Very different output frequencies occur at the same values of E , depending on the relative contributions of excitation and inhibition. For example, when $f_E = 3s$, $f_I = s$, the value of E is 6s and the mean spike frequency is 65. The same value of E occurs when $f_E = 2s$ and $f_I = 0$ but the frequency is only 37. At a given frequency of excitation, the ratio $f_E/(f_E + f_I)$

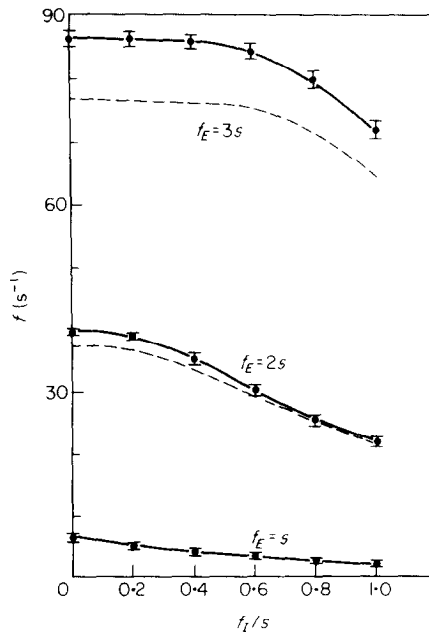


FIG. 2. Frequency of firing of the model neuron as a function of frequency of inhibition for three values of the frequency of excitation. Error bars indicate 95% confidence intervals for the mean intervals. The broken lines include the absolute refractory period.

seems to be a measure of the net excitation when epsp's and ipsp's have about the same amplitudes.

Figure 3 shows the effects of increasing amounts of inhibition on the variability of the interspike time. The standard deviation and the mean are plotted against f_I for the three values of the frequency of excitation. The results for the mean have already been considered in relation to the output frequency. The dependence of the standard deviation on f_I is qualitatively similar to that of the mean. For the case $f_E = s$ the standard deviation and the mean have almost the same magnitudes. For $f_E = 2s$ and $f_E = 3s$, however, the standard deviation begins to increase significantly before the mean, and the rate of change of the standard deviation with respect to f_I is greater. The mean and the standard deviation approach one another as f_I increases from zero and after a point of intersection the standard deviation becomes greater than the mean. Equivalently stated, the coefficient of variation of the interspike time is invariably less than one when $f_I = 0$, then increases as f_I increases to pass through unity and become greater than one when the inhibition is strong enough. Values of the coefficient of variation greater than

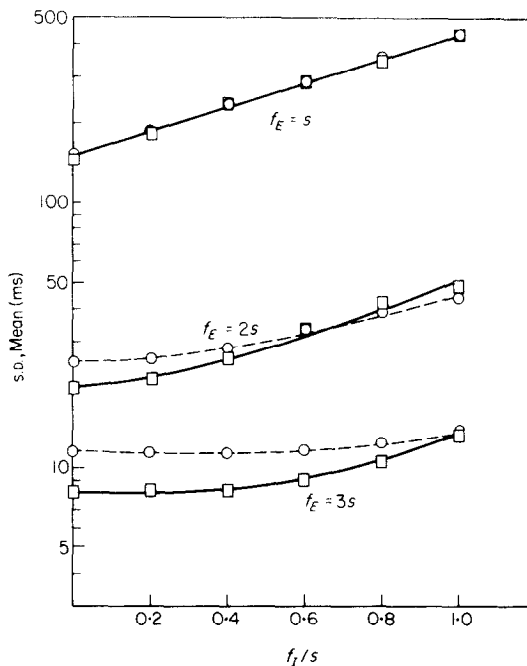


FIG. 3. Means (circles) and standard deviations (squares) of the interspike time as functions of inhibitory input frequency. The lines are visual best fits.

one have not, as far as we know, ever been obtained when there is (Poisson) excitation only. Thus a coefficient of variation >1 seems to be a unique manifestation of relatively large amounts of inhibition. It is noteworthy that coefficients of variation of the interspike interval greater than one have been found in several studies on spike trains of real neurons. Examples are provided by spontaneously active neurons of the ventrobasal complex of *cats* during sleep (Nakahama, Suzuki, Yamamoto, Aikawa & Nishioka, 1968), neurons in thalamic ventrolateral nucleus of *cat* in conditions of waking and slow and fast wave sleep (Lamarre, Filion & Cordeau, 1971), visual cortex neurons of rabbit (Velikaya & Kulikov, 1966) and hippocampal pyramidal cells of rabbit (Bassant, 1976). It seems likely that when a neuron has a trigger zone and has truly random synaptic inputs then one may infer the presence of a relatively large amount of inhibition if the interspike time has a coefficient of variation greater than unity. Further, if a neuron has an interspike interval with a coefficient of variation less than one whilst the animal is in a certain behavioural state whereas its value is greater than one in another behavioural state, then one infers that a relatively large number of inhibitory synaptic inputs are active in the second behavioural state.

(C) EFFECTS OF THE REVERSAL POTENTIALS

We have seen in section 3 that neglecting the excitatory reversal potential can lead to a considerable change in the calculated mean interval between action potentials. Computer simulations revealed the same qualitative effects. As a general rule, the longer the interval between firings the greater the difference in the results with $\alpha = 0$ and $\alpha = 1$ in equation (28). For the parameter values of the last subsection and with $f_E = 3s$, $f_I = 0$, mean intervals of 11.6 and 10.7 ms were obtained with and without the reversal potential. The difference is 7.8%. When $f_E = s$ and $f_I = s$, the means were 427 and 332 ms, a difference of 22.2%. The differences in the standard deviation were similar.

An explanation of the correlation between mean interval length and the difference in the results with and without the excitatory reversal potential is immediate. The longer the interspike time the greater the number of epsp's required to reach threshold and hence the greater the differences in the subthreshold depolarizations. The difference in $V(t)$ is always in the same direction with each arriving epsp, since the epsp amplitude is always greater when the reversal potential is ignored. In the various simulations with and without the excitatory reversal potential there were no qualitative differences in the interval histograms. Since the difference in firing rates may be quite

large for a given input process and different reversal potentials, especially in the case of a slowly firing neuron, it is remotely feasible that if all other relevant parameters were known, then the interspike interval data could reveal information on the reversal potentials for epsp's. This knowledge would be useful in identifying the excitatory neurotransmitter.

It might be thought that ignoring the inhibitory reversal potential ($\beta = 0$ in equation (28)) would always have a large effect on the interspike interval. One would suspect that a contributing factor is the ability of $V(t)$ to then wander off to large negative values. However, in most of the simulation studies we performed, including the inhibitory reversal potential made only a very small change in the moments of the interspike time. The differences were in fact more often than not statistically insignificant. For example, using the parameter values of the last subsection, when $f_E = f_I = s$, the mean and standard deviation were 427 and 423 ms for the model including the inhibitory reversal potential (with $\alpha = 1$), whereas the values were 429 and 446 ms without the inhibitory reversal potential. For a faster firing neuron the differences are also small. Mean intervals of 14.1 and 14.0 ms and standard deviations of 13.7 and 13.4 ms were obtained for $\beta = 1$ and $\beta = 0$, respectively, when $f_E = 3s$ and $f_I = s$.

There are two factors which make the inhibitory reversal potential have a relatively minor effect. Firstly, if the neuron is firing at reasonable rates (10 impulses/s or greater) then the depolarization does not spend much time at negative values and when $V(t)$ is negative the exponential decay acts in an excitatory fashion. This makes the excursions of $V(t)$ to large negative values unlikely under these conditions. Secondly, the inhibitory reversal potential is, in the cases mentioned, about the same distance from $V = 0$ as the threshold. In the model with $\beta = 1$, an ipsp arriving when $V < 0$ is smaller, and one arriving when $V > 0$ is larger than the ipsp elicited when $\beta = 0$. The latter ipsp has constant amplitude. Hence there is a compensatory effect and the subthreshold depolarizations at any instant are quite close. Even in some cases we examined where the values of θ and V_I were not symmetric with respect to $V = 0$, the interspike times differed only by negligible amounts. Appreciable effects of inclusion of V_I are expected to occur when inhibition is much more frequent than excitation. Simulation studies were performed with $s = (0.0058 \text{ s})^{-1}$, $V_E = 70$, $V_I = -5$, $a_E = 0.0456$, $a_I = 0.1$, $f_E = 460 \text{ s}^{-1}$, $f_I = 1000 \text{ s}^{-1}$, $\alpha = 1$, and a time decaying threshold $\theta(t) = 12 + 7.78 \exp(-t/0.023)$, t in sec. The mean and variance of the interspike time were 297 ms and 60,040 ms² with the inhibitory reversal potential whereas the values were 225 ms and 32,850 ms² when the reversal potential was ignored. Hence, under some circumstances, allowance for the inhibitory reversal potential can be quite an important factor.

I thank Warren Smith and Rod Sproule for the many simulations on which this work is largely based. Supported in part by NRC of Canada grant A 4559 to Robert Miura.

REFERENCES

- BASSANT, M. H. (1976). *Electroenceph. clin. Neurophysiol.* **40**, 585.
 BURKE, R. E., FEDINA, L. & LUNDBERG, A. (1971). *J. Physiol. (Lond.)* **214**, 305.
 BURNS, B. D. & WEBB, A. C. (1976). *Proc. R. Soc. Lond. B.* **194**, 211.
 COPE, D. K. & TUCKWELL, H. C. (1979). *J. theor. Biol.* (in press).
 ECCLES, J. C. (1957). *The Physiology of Nerve Cells*. Baltimore: Johns Hopkins.
 EIDE, E., FEDINA, L., JANSEN, J., LUNDBERG, A. & VYKLYCKY, L. (1969). *Acta physiol. scand.* **77**, 125.
 GOEL, N. S., RICHTER-DYN, N. & CLAY, J. R. (1972). *J. theor. Biol.* **34**, 155.
 HODGKIN, A. L. & HUXLEY, A. F. (1952) *J. Physiol. (Lond.)* **117**, 500.
 HOLDEN, A. V. (1976). *Models of the Stochastic Activity of Neurones*. Berlin: Springer.
 JACK, J. J. B., MILLER, S., PORTER, R. & REDMAN, S. J. (1971). *J. Physiol. (Lond.)* **215**, 353.
 JANSEN, J. K. S., NICOLAYSEN, K. & RUDJORD, T. (1966). *J. Neurophysiol.* **29**, 1061.
 JASWINSKI, A. H. (1970). *Stochastic Processes and Filtering Theory*. New York: Academic Press.
 JOHANNESMA, P. I. M. (1968). In *Neural Networks* (E. R. Cainiello, ed.). Berlin: Springer.
 KRNEVIC, K. (1974). *Physiol. Rev.* **54**, 418.
 LAMARRE, Y., FILION, M. & CORDEAU, J. P. (1971). *Exp. Brain Res.* **12**, 480.
 MOLNAR, C. E. & PFEIFFER, R. R. (1968). *Proc. IEEE* **56**, 993.
 NAKAHAMA, H., SUZUKI, H., YAMAMOTO, M., AIKAWA, S. & NISHIOKA, S. (1968). *Physiol. Behav.* **3**, 745.
 RALL, W. (1964). In *Neural Theory and Modeling* (R. F. Reiss, ed.). Stanford University Press.
 ROY, B. K. & SMITH, D. R. (1969). *Bul. math. Biophys.* **31**, 341.
 SKOROHOD, A. V. (1965). *Studies in the Theory of Random Processes*. Reading: Addison-Wesley.
 STEIN, R. B. (1965). *Biophys. J.* **5**, 173.
 TUCKWELL, H. C. (1975). *Biol. Cybernetics* **18**, 225.
 TUCKWELL, H. C. (1976). *J. appl. Prob.* **13**, 39.
 TUCKWELL, H. C. (1977). *J. theor. Biol.* **65**, 783.
 TUCKWELL, H. C. (1978). *Biophys. J.* **21**, 289.
 TUCKWELL, H. C. & RICHTER, W. (1978). *J. theor. Biol.* **71**, 167.
 VELIKAYA, R. R. & KULIKOV, M. A. (1966). *Biofizika* **11**, 321.
 WAN, F. Y. M. & TUCKWELL, H. C. (1979). *Biol. Cybernetics* (submitted).
 YANG, G. L. & CHEN, T. C. (1978). *Math. Biosciences* **38**, 1.

APPENDIX

Equation (9) can be generalized to handle an arbitrary distribution of amplitudes of postsynaptic potentials rather than just epsp's and ipsp's of single amplitudes. The depolarization will satisfy the stochastic equation

$$dV = -sV dt + \int_{(-\infty, \infty)} g(u, V)N(dt, du). \quad (\text{A1})$$

Here $N(t, du)$ is a Poisson process (random measure) with expectation $f(du)t$, so that f is the rate measure. $N(t, du)$ is the number of events up to time t

falling in the set $(u, u + du)$. The function g is defined by

$$g(u, V) = \begin{cases} u(V_E - V), & u > 0, \\ 0, & u = 0, \\ -u(V_I - V), & u < 0. \end{cases} \quad (\text{A2})$$

Suppose that $f(du)$ has a density so that $f(du) = \phi(u) du$ and let the total mean rate of synaptic events (of any amplitude) be

$$R = \int \phi(u) du. \quad (\text{A3})$$

To distinguish excitatory from inhibitory events set

$$\phi(u) = \begin{cases} \phi_E(u), & u > 0, \\ \phi_I(u), & u < 0. \end{cases} \quad (\text{A4})$$

The equation for the expectation of the time at which $V(t)$ first reaches or exceeds threshold becomes the integrodifferential equation

$$-RF(x) - sxF'(x) + \int_{(0, \infty)} F(x + u(V_E - x))\phi_E(u) du + \int_{(-\infty, 0)} F(x - u(V_I - x))\phi_I(u) du = -1, \quad (\text{A5})$$

with the same constraints as (16). The generalization of the recursion relations for the higher moments is immediate.

The amplitudes of the postsynaptic potentials depend on $V(t)$ but it is useful to consider the distribution of amplitudes of these potentials elicited from rest ($V = 0$). Given that a synaptic event occurred, the probability that the postsynaptic potential has amplitude in the interval $(uV_E, [u + du]V_E)$ with u positive (excitatory event) is $\phi_E(u) du/R$, and the probability that the amplitude is in the interval $(-uV_I, -[u + du]V_I)$ with u negative is $\phi_I(u) du/R$. The special case considered in the text where there is inhibition of frequency f_I and excitation of frequency f_E is obtained when $\phi_E(u) = f_E \delta(u - a_E)$ and $\phi_I(u) = f_I \delta(u + a_I)$, and a_E and a_I both positive and $\delta(\cdot)$ is the Dirac delta function. As far as applications go, the most appropriate forms for ϕ_E and ϕ_I would be unimodal with gaussian type appearance centered on some mean value.