

Recurrent Inhibition and Afterhyperpolarization: Effects on Neuronal Discharge

Henry C. Tuckwell

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

Abstract. The inhibitory influences of recurrent inhibition and afterhyperpolarization are studied theoretically insofar as they affect the density of the interspike interval and the frequency transfer characteristic. The methods employed involve exact results for excitation with decay and constant threshold, computer simulations for decaying thresholds representing afterhyperpolarization, and the diffusion approximation for excitation with inhibition and a constant threshold. Afterhyperpolarization tends to preserve the linearity of the frequency transfer characteristic and the lognormality of the interspike time. Recurrent inhibition which grows linearly with frequency of excitation can lead to frequency limiting. Some forms of nonlinear recurrent inhibition may lead to a filter type effect whereby the neuron responds significantly only over certain ranges of input intensity. A simple network model is analysed which exhibits recurrent inhibitory frequency growing linearly with frequency of excitation. An estimate of 10 to 50 is made for the number of Renshaw cells which connect with a spinal motoneuron. The frequency limiting of motoneurons is discussed and the stabilizing influence attributed to Renshaw cells is questioned. It is postulated that Renshaw recurrent inhibition is of functional significance at low levels of excitatory drive to motoneurons and that its effect is diminished by reciprocal inhibition at high excitatory input frequencies.

1. Introduction

Motoneurons in the mammalian spinal cord receive a very large number of synaptic inputs. A recent study, based on light microscopic data on motoneuron sizes (Barrett and Crill, 1974) and electron microscopic data on the distribution of synaptic boutons (Conradi,

1969) revealed that the average alpha-motoneuron in the cat lumbosacral spinal cord has a total number of about 22,600 synaptic endings of which 12,000 are excitatory, the remaining 10,600 being inhibitory (Koziol and Tuckwell, 1978). If all these input processes were simultaneously active, the motoneuron could be receiving synaptic inputs at rates up to one million per second.

The neurophysiological and anatomical details of the connections of other neurons with such motoneurons are not yet fully known. Some of the established inputs which come from various synergist and agonist sources are (see for example, Eccles 1957 and 1969):

- i) Ia monosynaptic excitation,
- ii) Ia disynaptic excitation and inhibition,
- iii) Ib disynaptic excitation and inhibition,
- iv) Renshaw (recurrent) inhibition.

It is an extremely challenging theoretical problem to understand both qualitatively and quantitatively how the various synaptic inputs are integrated by the motoneuron in its spike production. In this article we will focus on Ia monosynaptic excitation and recurrent inhibition and investigate their combined effect on the input/output relationship of the motoneuron. We will also consider how afterhyperpolarization can affect both the frequency transfer characteristic and the shape of the density of the interspike time when inputs are random.

The curve marked *B* in Figure 1 shows the experimentally obtained mean output frequency, f , of spikes of a cat lumbosacral cord neuron undergoing Poisson excitation via chiefly the Ia monosynaptic pathway (Redman et al., 1968). The quantity f_e is the mean net input frequency of excitatory postsynaptic potentials (epsp's) from four independent stimulators. Let $X(t)$ be the random depolarization of the trigger zone of the motoneuron at time t after the previous

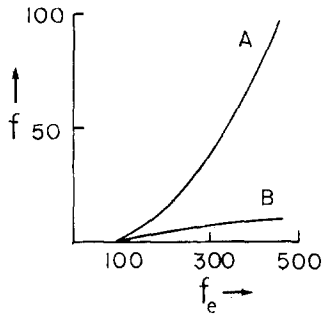


Fig. 1. Output frequency versus input frequency of Poisson excitation. The curve B is the experimental result for a cat tonic spinal motoneuron (Redman et al., 1968). Curve A is the calculated result assuming the neuron receives excitation only with fixed epsp amplitudes

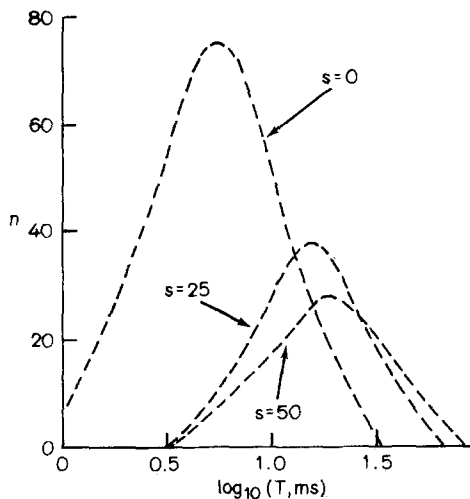


Fig. 2. Densities of the logarithm of the interspike interval from computer simulations for a neuron with excitation and a decaying threshold representing afterhyperpolarization. The quantity s is the time constant of decay of the threshold in msec. and n represents bin counts

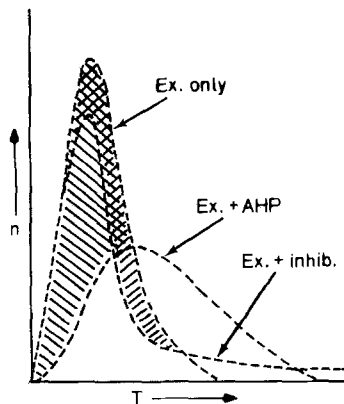


Fig. 3. Sketch of densities of the interspike interval based on computer simulations, contrasting the effects of afterhyperpolarization and postsynaptic inhibition. Hatched areas indicate those parts of the control density (excitation only) which are shifted to larger values of T

spike. Assuming the monosynaptic pathway is the only input source we may employ Stein's (1965) leaky integrator model whereupon we have

$$dX(t) = -\sigma X(t)dt + \varepsilon_e d\Pi(f_e; t), \quad (1)$$

where σ is the reciprocal of the membrane time constant, ε_e is the (average) epsp amplitude and $\Pi(f_e; t)$ is a temporally homogeneous Poisson process such that $\Pi(f_e; t) = 0$ and

$$\Pr\{\Pi(f_e; t) = k\} = \exp(-f_e t) (f_e t)^k / k!, \quad k = 0, 1, 2, \dots \quad (2)$$

Suppose the motoneuron under observation had average physiological properties; i.e. a threshold depolarization for firing of 12 mV (Calvin and Schwindt, 1972) and a time constant for decay of Ia epsp's of 5.8 ms (Jack et al., 1971). Upon calculating the expectation of the time for $X(t)$ as described by (1) to first reach threshold from rest (Tuckwell, 1976a), one finds that the experimental and predicted firing rates are equal at the lowest frequency of excitation ($f_e = 140 \text{ s}^{-1}$) only if the average epsp amplitude, ε_e , is about 3.2 mV. This amplitude was not measured in the cited experiment but the value 3.2 mV is compatible with the conditions of stimulation and known epsp amplitudes in this kind of neuron for Ia monosynaptic excitation in various experimental arrangements (Curtis and Eccles, 1959; Jack et al., 1971).

If one proceeds to calculate the output frequency for increasing input frequencies f_e with epsp's of amplitude 3.2 mV, one obtains the curve marked A in Figure 1. Clearly there is a great difference between the mean frequency of action potentials so obtained and the observed frequency. When $f_e = 460 \text{ s}^{-1}$ the calculated frequency is about ten times the experimental result. The difference in f values of curves A and B measures the inhibitory influences on the motoneuron as a function of f_e , though some inhibitory influences are probably in operation at small f_e .

It is natural to ask what factors are responsible for the observed depression of f as f_e increases. The situation is extremely complicated because there are many extrinsic and intrinsic inhibitory influences. These include afterhyperpolarization, recurrent inhibition via Renshaw cells, presynaptic inhibition, epsp amplitude dependence on f_e (see the next paragraph) and postsynaptic inhibition through various interneurons. We are unable to ascertain the precise roles of these effects with respect to the aforementioned experiment but will consider some of them in the search for general principles in the firing patterns of neurons with random synaptic bombardment.

In some unpublished studies involving simulations of motoneuron spiking under stochastic Ia excitation

(Morjanoff, 1971) it was found that the frequency limiting exemplified by curve *B* of Figure 1 could be explained by decreasing the epsp amplitudes at high f_e in accordance with the diminution observed in the Ia excitation experiments of Curtis and Eccles (1960). That diminution, however, was in the terminal response of a steady state set up by regular repetitive stimulation. A recent calculation (Walsh and Tuckwell, 1978) has shown that such diminution is consistent with an epsp generated by a constant current pulse, the decreased terminal response being merely a manifestation of the dependence of the steady state on stimulus frequency. When epsp's occur randomly, steady state conditions will not prevail and the diminution of response seen in Curtis and Eccles' (1960) experiment will not occur to the same extent. Nevertheless, since the model used to generate the output frequencies of curve 1A has constant epsp amplitudes, it is clear that some of the depression to curve 1B could be attributed to the decreased epsp amplitude that occurs at increased subthreshold depolarizations.

The maximum rate of firing of the experimental preparation of Figure 1 is about 10 s^{-1} , which is about the maximum frequency observed for many tonic alphanotoneurons during static muscle stretch at various lengths (Meyer-Lohmann et al., 1976). This implies that the neuron under consideration was probably of this type. A maximal group I afferent volley in the posterior biceps—semitendinosus nerve usually leads to a depression of the monosynaptic Ia epsp in a gastrocnemius—soleus motoneuron which is greatest (about 10%) if the conditioning volley precedes the test volley by about 20 ms (Eccles et al., 1961c). A sequence of 22 supramaximal conditioning volleys at 210 s^{-1} led to a depression of the Ia monosynaptic epsp to about 25% of its control value and recovery occurred after about 600 ms. For the motoneuron of curve 1B, the experimental and calculated output frequencies with random excitation alone agree at $f_e=460\text{ s}^{-1}$ if the epsp amplitude is 1.9 mV:—that is, a reduction to 59% of its 'control' value. Presynaptic inhibition could, therefore, lead to the differences between curves 1A and 1B under certain stimulus conditions. It is noted, however, that the motoneuron under consideration was stimulated by inputs along a few fibers of the gastrocnemius-soleus nerve. An early experiment (Eccles, et al., 1961c) showed that stimulation of group I fibers from gastrocnemius-soleus produced negligible presynaptic inhibition in all motoneurons tested, though a more recent study (Decandia et al., 1967) has cast some doubt on this result. We will not concern ourselves further with presynaptic inhibition in this report: our focus will be on afterhyperpolarization and recurrent inhibition.

2. Afterhyperpolarization

Afterhyperpolarization, attributed to increased K^+ conductance in spinal motoneurons (Gustaffson, 1974) contributes to an elevated threshold depolarization for firing following spike generation. Various time dependent thresholds have been employed in modelling the response of neurons to stochastic stimulation (Holden, 1976). The form chosen in the present study is

$$\theta(t) = \begin{cases} \infty, & 0 < t < T_R \\ k_1 + k_2 \exp(-(t - T_R)/s), & t \geq T_R \end{cases} \quad (3)$$

where T_R is the absolute refractory period (about 1 ms for many CNS neurons) and s is the time constant of decay of threshold, t being the time since the preceding spike.

Computer simulations were performed for the model neuron whose subthreshold depolarization is given by (1) and whose threshold for firing is given by (3). A mean input frequency $f_e=500\text{ s}^{-1}$, a time constant of decay $\sigma^{-1}=5.8\text{ ms}$ and an epsp amplitude $\varepsilon_e=4\text{ mV}$ were employed. Figure 2 shows the densities of interspike intervals with time plotted logarithmically for threshold parameters $T_R=1\text{ ms}$, $k_1=12\text{ mV}$, $k_2=10\text{ mV}$ and values of $s=0$ [corresponding to no afterhyperpolarization (AHP)], 25 and 50 ms. For each value of s a total of 1000 simulated spikes was obtained. The densities shown are hand drawn best fits through bin counts. With no AHP the mean firing frequency is 89 s^{-1} , which can be compared with the corresponding values of 41 s^{-1} for $s=25\text{ ms}$ and 24 s^{-1} for $s=50\text{ ms}$ (slowly decaying threshold).

The probability densities of the logarithm of the interspike interval for the various rates of decay of the afterhyperpolarizing current are in each case considered here approximately normal curves. Apparently AHP coupled with excitation does not alter this feature of the interval distribution. The modes of the densities shown in Figure 2 are 6, 15, and 21 ms respectively. Thus both the means and the modes are significantly increased as the time constant of decay of the threshold increases.

It is interesting to compare the effects of AHP and postsynaptic inhibition. The latter tends to significantly increase the mean but not necessarily the mode (Tuckwell, 1978) whereas both are increased by AHP. Postsynaptic inhibition can, in appreciable amounts, destroy the approximate lognormality (if it was present) of the interspike time by producing an excess of long intervals. AHP tends to preserve the lognormality—at least in the cases we have examined. It should be pointed out that the issue of lognormality first arose because Burns and Webb (1976) discovered neurons in cerebral cortex of cat whose interspike

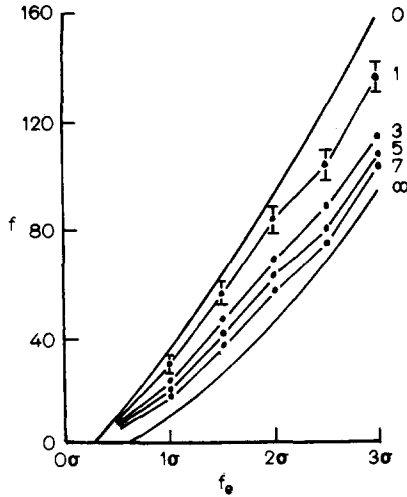


Fig. 4. Frequency transfer characteristics for a model neuron with excitation and various degrees of afterhyperpolarization. The solid curves are exact results (constant thresholds) whereas filled circles are from simulations. The number to the right is the time constant of decay of the threshold in units of the membrane time constant. The error bars represent 95% confidence limits and the frequency of excitation is in units of the reciprocal of the membrane time constant

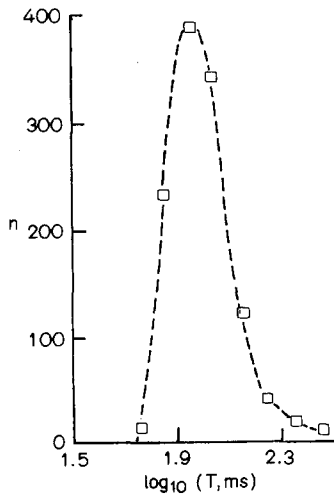


Fig. 5. Bin counts of the logarithm of the interspike interval for a cat spinal motoneuron with Poisson excitation (based on Morjanoff, 1971; results of Redman et al., 1968)

times were either lognormal or suffered a violation of lognormality in the tail.

To illustrate the comparative effects on the density, Figure 3 is a sketch of typical densities encountered in the three cases; (a) constant threshold with excitation only, (b) constant threshold with excitation and inhibition in accordance with

$$dX(t) = -\sigma X(t)dt + \varepsilon_e d\Pi(f_e; t) - \varepsilon_i d\Pi(f_i; t) \quad (4)$$

where f_i is the inhibitory mean rate and ε_i is the ipsp amplitude, and (c) decaying threshold with excitation only. Shaded portions indicate those parts of the control density (a) which are shifted to longer intervals

by these two inhibitory processes. It can be seen that the major part shifted by postsynaptic inhibition is at values greater than the mode. AHP, on the other hand, removes chiefly that part of the density which occurs less than the modal interval though some is also deleted at longer interspike times. If we now imagine both of these inhibitory processes acting together, (though of course there is no linearity operating here) we can see that their combined effect will be to produce a more symmetric, and in fact (except for the tail) more Gaussian type density. This aspect will be further discussed in the last section.

In order to examine the effects of AHP on the frequency transfer characteristic (i.e. the plot of f versus f_e) when epsps arrive randomly, computer simulations were again performed for the model system consisting of (1) for the membrane depolarization and (3) for the threshold depolarization. Since a large number of simulations were to be performed, an epsp amplitude of 5 mV was chosen which represents a large fraction of the threshold with parameters $k_1 = 10$ mV, $k_2 = 5$ mV and $T_R = 0$. The membrane time constant was again $\sigma^{-1} = 5.8$ ms, the time constants of decay of threshold being c times 5.8 ms with $c = 1, 3, 5$ and 7 in separate runs.

The results obtained are shown in Figure 4, where values of the output frequency f are plotted for excitation frequencies of $f_e = \sigma, 1.5\sigma, 2\sigma, 2.5\sigma$, and 3σ . The value of c is to the right of each characteristic. The error bars on the curve for $c=1$ represent 95% confidence limits for the mean interspike time and have been omitted for $c=3, 5$ and 7 to avoid overcrowding on the figure. The results for $c=0$ and $c=\infty$, which correspond to constant thresholds of 10 and 15 mV respectively, were not obtained by computer simulation but from the exact calculated results determined by solving the relevant differential-difference equation (Tuckwell, 1976b). The results for intermediate values of c lie between the exact results which provides a useful check on the accuracy of the simulation studies. This same check applied on the accuracy of the simulation studies. This same check applied to the coefficients of variation of the interspike time. This expected check is of course a consequence of the inequality, for finite positive values of the time constant of decay of the threshold ($\theta(t)$),

$$T_{k_1} < T_{\theta(t)} < T_{k_1 + k_2},$$

where T_k denotes the first time the depolarization reaches k .

The main observation, however, is that AHP has not much effect on the overall shape of the f versus f_e curve. The results indicate a nearly linear input/output relation (in the absence of frequency limiting by abso-

lute refractoriness) of the kind observed in experimental current injection into cat spinal motoneurons (Kernell, 1965). There is no evidence of any frequency limiting of the kind seen in Figure 1B. Thus AHP, in the cases considered, tends to preserve the lognormality of the interspike time and the linearity of the frequency transfer characteristic, if these properties are present with excitation and a constant threshold. We note that approximate linearity over wide ranges of input frequency of excitation had been found in previous stochastic modelling of neural firing by Goldberg et al. (1964) and Geisler and Goldberg (1966) who adopted a different formalism for both the random input process and the threshold function.

3. Recurrent Inhibition

It is not possible to deduce what inputs were operative for the motoneuron of Figure 1B apart from the deliberately stimulated Ia excitatory pathway. Figure 5 shows the density of the logarithm of the interspike interval for a similar neuron in the same experimental arrangement at a nominal stimulus rate of 78 s^{-1} . This density is based on results of Redman et al. (1968) as given by Morjanoff (1971). A test for normality of this density using bin counts gave a value of $\chi^2 = 215$ with 5 degrees of freedom ($p = 0.0000$). Thus the interspike time is almost certainly not lognormal. As can be seen by inspection the violation of lognormality is due to a preponderance of long intervals so that one concludes that the neuron was receiving postsynaptic inhibition.

We now ask the following (hypothetical) questions. If the depression of curve 1A to 1B was due to inhibitory postsynaptic potentials generated in the motoneuron, what could one say about the functional relationship between the frequency of inhibition and the frequency of excitation? Further, if this inhibition is attributed to the Renshaw circuit, can its strength be deduced by considering a simple model of the anatomical connections?

To answer the first of these questions, suppose in addition to Poisson arriving epsp's of amplitude 3.2 mV at frequency f_e , random ipsp's occur with mean rate f_i and mean amplitude ε_i . Exact calculations for the mean interspike interval for subthreshold depolarizations given by (4) and constant threshold do not appear possible and computer simulations would not be feasible for the large number of results needed. Hence we turned to the diffusion approximation,

$$dX(t) = (-\sigma X(t) + f_e \varepsilon_e - f_i \varepsilon_i) dt + (f_e \varepsilon_e^2 + f_i \varepsilon_i^2)^{\frac{1}{2}} dW(t), \quad (5)$$

where $W(t)$ is standard Brownian motion. The mean interspike interval for this model can be obtained by

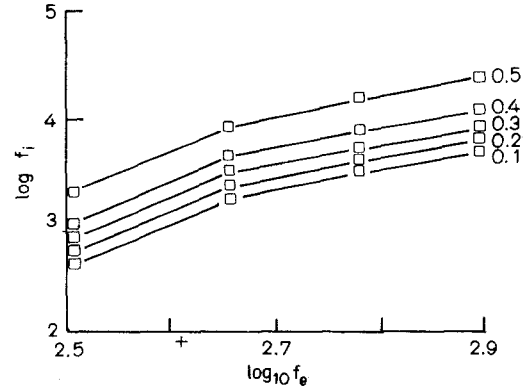


Fig. 6. Calculated frequencies of ipsp's, obtained from the diffusion approximation, which at the various frequencies of excitation cause the depression of curve A to curve B in Figure 1. The number to the right is the ipsp amplitude in mV

the Roy and Smith (1969) formula,

$$E[T] = \sigma^{-1} \left[\sum_{k=0}^{\infty} \frac{2^k}{(2k+1)!(k+1)} (Y^{2k+2} - Z^{2k+2}) + 2\sqrt{\pi} \{Z\phi(Z^2) - Y\phi(Y^2)\} \right] \quad (6)$$

where for a threshold θ ,

$$Y = (a - \sigma\theta)/b\sigma^{1/2}, \quad (7)$$

$$Z = a/b\sigma^{1/2}, \quad (8)$$

with $a = f_e \varepsilon_e - f_i \varepsilon_i$, $b = (f_e \varepsilon_e^2 + f_i \varepsilon_i^2)^{\frac{1}{2}}$ and $\phi = \phi(\frac{1}{2}, 1.5; u)$ is the confluent hypergeometric function of the first kind,

$$\phi(p, q; u) = 1 + \frac{pu}{q} + \frac{p(p+1)u^2}{q(q+1)2!} + \dots \quad (9)$$

For a given f_e and ε_i we computed the expected output frequency (i.e. reciprocal of $E[T]$) for various values of f_i . By graphical methods the particular value of f_i was found which gave rise to the value of f in curve 1B at the given f_e . The resulting values of f_i are shown in Figure 6 for assumed ipsp amplitudes $\varepsilon_i = 0.1, 0.2, 0.3, 0.4,$ and 0.5 mV and for $f_e = 320, 460, 600$ and 790 s^{-1} . The smallest of these f_e values was considered a reasonably safe one to commence using the diffusion approximation. For the last two values of f_e , the value of f was obtained by extrapolating the experimental results for Poisson stimulation using the asynchronous stimulation results as a guide.

It can be seen that the frequency of ipsp's needed to depress curve 1A to 1B is approximately a linear function of the mean frequency of epsp's. The slopes of the f_i versus f_e curves do not here depend significantly on the mean amplitude chosen for the ipsp's. Hence the frequency transfer characteristic represented by curve 1B would result if f_i is proportional to f_e . Though no definite statements appear possible, owing to the large

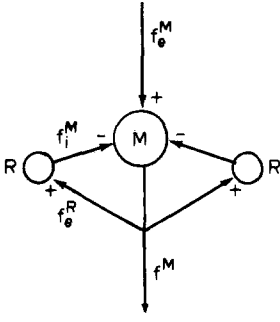


Fig. 7. Simple recurrent inhibitory network involving the motoneuron pool M and the Renshaw cells R . Excitatory and inhibitory synapses are denoted + and -

number of assumptions made in the calculations, there is noteworthy agreement between this theoretical result and experimentally measured rates of Renshaw cell tonic discharge frequencies at various lengths of static stretch of the triceps surae muscle. In one study (Hellweg et al., 1974) an almost linear relation was found between the mean increase in Renshaw cell (RC) discharge frequency and muscle extension. In another experiment (Pompeiano and Wand, 1976) a linear relation was found between increase in Renshaw cell discharge rate (relative to spontaneous activity) and frequency of action potentials in Ia fibers.

To answer the second question we must consider the details of the actions of RC on motoneurons. RC are apparently *excited* only by motoneuron collaterals (Hellweg et al., 1974), though they do receive other inputs including inhibition from RC resulting in reciprocal inhibition (Belcher et al., 1976; Wilson et al., 1964). A given motoneuron receives RC inhibition when several muscle nerves are stimulated, the amplitude of the ipsp being greatest usually when its own muscle nerve is stimulated (Eccles et al., 1961a). Thus RC receive excitation from many motoneurons in various nuclei and in turn have widespread synaptic connections with motoneurons.

In early studies (e.g., Eccles et al., 1961b) of RC discharge patterns (which determine the sequence of ipsp's in motoneurons) ventral root stimulation was employed. A typical RC response was a burst of spikes of which about 20 occurred in the first 45 ms after arrival of the volley at the cord (Goldfarb, 1976) with an initial frequency which may be 1000 s^{-1} or higher (Eccles, 1969). Such RC bursting is also found during dynamic muscle stretch if the rate of increase in length is high enough (Hellweg et al., 1974; Meyer-Lohmann et al., 1976). Under conditions of static stretch, however, many RC exhibit tonic discharges and the superposition of many such spike trains will result in a sequence of ipsp's in a motoneuron which will closely resemble a Poisson process. Many RC also discharge "spontaneously" with rates as high as 20 s^{-1} with a

recently reported mean rate of 6 s^{-1} (Goldfarb, 1976). It is also pointed out that whereas tonic motoneurons are more susceptible to RC inhibition than larger phasic motoneurons (Granit, 1963; Hellweg et al., 1974), RC tend to be more responsive to activity in phasic motoneurons which probably explains the RC burst response to dynamic muscle stretch.

It seems reasonable to conclude that the tonic motoneuron of Figure 1B did receive random ipsp's from RC. Spontaneous RC spiking could explain the lack of motoneuron discharge at the lowest Ia frequency of asynchronous stimulation. Figure 7 depicts in a simplified way (that is, many other known connections in this local circuit are omitted) the relation between RC and motoneurons. The symbols M and R represent many motoneurons and RC respectively, and + and - indicate excitatory and inhibitory connections. Let f^M and f^R denote mean spike frequencies for such cells in a tonic situation and let subscripts e and i indicate excitation and inhibition. In the depicted situation RC discharge rate depends only on f_e^R , so $f^R = f^R(f_e^R)$. Motoneuron spike rate depends on both excitatory and inhibitory inputs so $f^M = f^M(f_e^M, f_i^M)$. Thus

$$df^M = \frac{\partial f^M}{\partial f_e^M} df_e^M + \frac{\partial f^M}{\partial f_i^M} df_i^M. \quad (10)$$

The input frequency of excitation to the RC is proportional to the motoneuron discharge frequency so $df_e^R = c_1 df^M$ with c_1 a constant. We may assume (Tuckwell, 1976b) a linear dependence of output frequency on excitatory input frequency which gives $df^R = c_2 df_e^R$, where c_2 is another constant. For the given network, motoneurons receive inhibition only as a consequence of RC spiking so that $df_i^M = c_3 df^R$, c_3 being a third constant. Substituting in (10) and rearranging terms gives

$$\frac{df_i^M}{df_e^M} = \frac{\partial f^M / \partial f_e^M}{(c_1 c_3 / c_2) - \partial f^M / \partial f_i^M}. \quad (11)$$

Suppose we insert the empirical relation of linearity between f_i^M and f_e^M by setting $df_i^M / df_e^M = k$ and put $c_1 c_3 / c_2 = c$. This gives the first order partial differential equation

$$\frac{\partial f^M}{\partial f_e^M} + k \frac{\partial f^M}{\partial f_i^M} = kc. \quad (12)$$

Solutions of this equation can be written

$$f^M = (ck/a) f_e^M + c(1 - 1/a) f_i^M \quad (13)$$

where a is a constant which must satisfy $0 < a < 1$ in order that increasing inhibition give rise to decreasing output frequency. When $f_e^M = 0$, (13) will give rise to negative output frequencies which must be taken to

mean zero. The solutions of (13) for various f_i^M are linear functions of f_e^M with the same slope. This is consistent with the empirical finding that motoneuron firing rate is a linear function of depolarizing current with the same slope for various levels of hyperpolarizing currents (Granit et al., 1966). The simple network for the connections of motoneurons with RC seems therefore to be quite consistent with the experimental and theoretical finding of a linear relation between recurrent inhibitory feedback frequency to the motoneuron and its afferent frequency of excitation.

There does not seem to be an available figure for the number of Renshaw cells which connect with motoneurons. We can make a rough estimate of an *upper bound* of the number of RC which exert recurrent inhibition on a motoneuron of the type we have considered. According to one source (Eccles, 1969) a single RC spike leads to an ipsp of about 0.3 mV in a motoneuron. This should be corrected to about 0.5 mV to allow for the AHP in that experiment (Eccles et al., 1961a). With this ipsp amplitude our calculation indicated that the motoneuron received ipsp's at about 1800 s^{-1} when its output frequency was 10 s^{-1} . At this kind of output rate for alpha motoneurons in one study (Meyer-Lohmann et al., 1976) Renshaw spiking occurs at mean rates of about 16 s^{-1} , with considerable variability, over and above spontaneous spiking, whose rate is about 18 s^{-1} [(the average from two different studies (Goldfarb, 1976; Pompeiano and Wand, 1976)]. Dividing the frequency of ipsp's by RC spike frequencies gives about a maximum number of 50 Renshaw cells connecting with an alpha motoneuron. Some recent (unpublished) computer simulations indicate that the diffusion approximation on which our estimate of ipsp frequency is based leads to an overestimate of this frequency and the number of connecting RC is to be corrected to about 25. Allowing for the other inhibitory influences will bring a more realistic estimate of about 10 which seems consistent with the maximal recurrent ipsp's generated in motoneurons and the ipsp amplitude due to a single RC spike. Hence the number of RC connecting with a given motoneuron is probably between 10 and 50 with more likelihood being attached to the lower end of this range of values.

We have seen that the frequency transfer characteristic is almost linear in the absence of inhibition, whereas with inhibition which grows in proportion to the frequency of excitation, the output frequency may saturate at a value much less than that imposed by absolute refractoriness. The question naturally arises as to what would happen if the inhibitory input frequency was a nonlinear function of the frequency of excitation. Figure 8 shows a hypothetical frequency transfer characteristic calculated from the

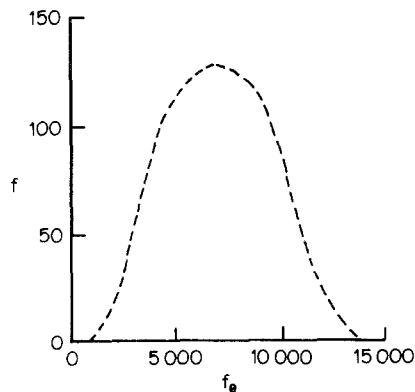


Fig. 8. Hypothetical frequency transfer characteristic, based on the diffusion formula, for a neuron whose frequency of recurrent inhibition is a nonlinear function of the afferent frequency of excitation

diffusion approximation using a mean epsp amplitude of 1 mV, an ipsp amplitude of 0.3 mV and with inhibitory frequency related to excitatory frequency by the nonlinear relation $f_i = f_e \exp(0.0001 f_e)$. It can be seen that with increasing f_e , the output frequency at first increases, reaches an upper limit and then declines to negligible values. The output frequencies of some cells exhibit this kind of behaviour an example being provided by the discharge frequency of squid optic nerve as light intensity increases (Lange and Hartline, 1974). One can imagine that if the frequency of inhibition grew sufficiently fast with f_e , the output frequency could be appreciable over a very narrow range of f_e and the cell would be a highly sensitive detector of certain input intensities only.

4. Conclusions

We have attempted to understand how various inhibitory influences, in particular AHP and recurrent inhibition, affect the pattern of discharges of a neuron with random synaptic input. The starting point was the set of experimental results for cat spinal motoneurons where at least one input, via the Ia pathway, was under experimental control. Based on the results obtained here and in some previous studies our main conclusions are as follows.

(1) With excitation only and constant threshold (no AHP) the input/output frequency relation of a neuron is linear over fairly wide ranges. Frequency limiting occurs only when the maximal firing rate imposed by absolute refractoriness is approached. The interspike interval is often an approximately log-normal random variable.

(2) With excitation only and AHP represented by a decaying threshold, the input/output relation is still approximately linear over wide ranges and the log-normality of the interspike time is not violated. The main functional significance of the AHP seems to be

the deletion of short interspike times (note that the interspike intervals in Redman et al.'s experiments were never less than about 50 ms). This ensures that the neuron never fires two spikes within a certain time interval and seems an important requirement if timing with respect to a target is needed.

(3) Presynaptic inhibition, because its primary effect is a decreased epsp amplitude, will tend to preserve the lognormality of the interspike time in both the presence and absence of AHP. If the reduction of epsp amplitude is a suitable increasing function of the afferent frequency of excitation, then, as demonstrated by simulation studies (Marjanoff, 1971), frequency limiting of the discharge rate may occur.

(4) Recurrent postsynaptic inhibition, if sufficiently strong, leads to a violation of the lognormality of the interspike time. This is due to an excess of long intervals. If the frequency of recurrent inhibition is a linearly increasing function of the frequency of excitation, then frequency limiting may occur at values below that imposed by absolute refractoriness. A nonlinear relation between recurrent inhibitory frequency and frequency of excitation may lead to a frequency transfer characteristic which rises to a maximum and then declines to zero.

It is an open question as to what causes frequency limiting in spinal motoneurons. Also unexplained is the apparent normality of the interspike interval in both cat motoneurons (and its near invariance over wide ranges of afferent frequencies of excitation) (Redman et al., 1968; Morjanoff, 1971) and human motor units (Clamman, 1969).

There is a puzzling aspect of the experimental results of Redman et al. (1968) for cat motoneurons. We have seen that the logarithm of the interspike time in one case for a nominal stimulus rate of excitation of 78 s^{-1} is not a normal random variable and concluded that postsynaptic inhibition was present. However, when the nominal stimulus rate of excitation was higher (e.g. 200 s^{-1}) a statistical test showed that lognormality of the interspike interval could not be rejected. One would have to conclude under these circumstances that the inhibition was relatively weak. A possible explanation for the diminished effect of recurrent inhibition is the known reciprocal inhibition between Renshaw cells.

If it is true that as the network involving Renshaw cells and motoneurons is driven harder, the inhibitory influence of the Renshaw cells (which we know are spiking faster (Pompeiano and Wand, 1976) does not grow significantly, then the idea that Renshaw cells exert a stabilizing influence on motoneuron discharge must be questioned. What then would be the significance of the Renshaw circuit? A possible answer is that spontaneous Renshaw spiking prevents spurious mo-

toneuron spiking until a "meaningful" afferent signal reaches the motoneurons. That is, the Renshaw circuit is only functional at low levels of excitatory drive to the motoneuron and other inhibitory influences cause the frequency limiting of motoneuron discharge rate at higher levels of excitation. It would be extremely interesting to see an experimental study of motoneuron discharge at various frequencies of Ia excitation when the glycine mediated Renshaw-motoneuron synapses are blocked by strychnine.

Acknowledgements. I thank Christopher Falk, Christopher L. Hermansen, Warren C. Smith and Rod. R. Sproule for computational assistance. Dr. S. J. Redman kindly provided data and useful correspondence. I also thank Drs. A. J. Petkau and J. A. Koziol for useful discussion. Supported in part by NRC of Canada grant A-4559 to Dr. R. M. Miura.

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Received: May 22, 1978

Dr. H. C. Tuckwell
Dept. of Mathematics Univ. of British Columbia
2075 Wesbrook Mall
Vancouver B.C., Canada V6T 1W5

Note added in proof: The general solution of (12) can be written $f^M = (kc/2)f_e^M + (c/2)f_i^M + g(f_e^M - f_i^M/k)$ where g is an arbitrary differentiable function. To see what this function should be we note from experimental results (Kernel, 1965) and previous calculations, that in the absence of inhibition, f^M is proportional to f_e^M . Hence we must have $g(f_e^M) = k_1 f_e^M$ and the particular solution of interest is as given by (13) with $k_1 = kc(a^{-1} - 2^{-1})$. I thank Robert Miura for pointing this out.