A MODEL FOR THE VARIABILITY OF INTERSPIKE INTERVALS DURING SUSTAINED FIRING OF A RETINAL NEURON

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ABSTRACT The statistics of the variability of interspike intervals of ganglion cells in the retina of goldfish are modeled by assuming the noise in an integrate-and-fire mechanism is proportional to the reciprocal of a normally distributed variable. This model meets the constraint that the coefficient of variation of the interspike intervals does not change when the mean firing rate of the neuron changes. Alternative sources of variability of interspike intervals are discussed.

INTRODUCTION

Under steady stimulation, the firing patterns of sensory neurons show evidence of considerable variability. In the last two decades, investigators have examined the first-order statistics of maintained firing patterns with the goal of characterizing the processes responsible for this variability.

This study is concerned with modeling the first-order statistics of the firing patterns of a particular sensory neuron: the retinal ganglion cell of the goldfish. The model we shall discuss is designed to accommodate the constraints imposed by findings we reported in a recent study (Levine and Shefner, 1977*b*). In that study, we examined the variability of interspike intervals (ISIs), which we characterized by the coefficient of variation ($C \equiv$ standard deviation of ISIs/mean ISI). We observed the properties of C over long periods of time with respect to the changes in mean firing rate due to stimulation of the retina and those due to drifts. The results of this study indicate that C is essentially independent of the firing rate of the cell; this independence cannot easily be accounted for by existing models for the generation of ISIs. We cannot identify the natures of the independent mechanisms implicated, but we can say that, at least in this neuron, the signal responsible for increases or decreases in the mean level of activity of the cell must effectively multiply (or divide) the output of the mechanism or mechanisms principally responsible for the variability of the ISIs. This requirement served as the starting point for our speculations about physiologically realizable mechanisms that could be responsible for the variability of firing patterns in this neuron.

A MODEL FOR THE GENERATION OF ISI HISTOGRAMS

In its simplest form, our model assumes that the input to the ganglion cell from more distal units does not contribute to the variability of the ISIs. That is, the synaptic activation of the cell, which determines the mean rate at which action potentials are produced, is essentially a constant over the period in which ISI statistics are being examined. We assume that the variability of the ISIs is intrinsic to the ganglion cell, and that this variability multiplies a steady input. It should be noted that this is not a requirement; the commutative nature of multiplication makes equivalent all models in which the variability multiplies the input, regardless of the level of the multiplication. However, Schellart and Spekreijse (1973) have presented convincing evidence that the source of most of the variability of ISIs in goldfish retinal ganglion cells lies within the ganglion cell itself.

Consider an electrical model of the ganglion cell. If the input is considered to be a current, i, it can be divided between a membrane leakage resistance, R_ℓ, and the resistance, R_g, of the part of the neural membrane that is the spike-generating mechanism. The current passing into the spike-generating mechanism, and thus contributing to the generation of an action potential, will be

$$i_{\text{effective}} = iR_\ell/(R_\ell + R_g). \tag{1}$$

A simple model for converting this effective current into spikes is the integrate-and-fire model (e.g. Knight, 1972; Stein et al., 1972); in this model, the current is integrated for a period of time τ (the ISI) until a threshold charge (ρ) is reached.[1] At this point, an action potential is produced, and the integrator resets to 0. If the input current is constant, as we are assuming, and there is no noise, the integral is a straight line whose slope is given by the value of that constant. That is,

$$i_{\text{effective}} \cdot \tau = \rho, \tag{2}$$

or

$$\tau = (R_g/R_\ell + 1)\rho/i. \tag{3}$$

If $R_g \gg R_\ell$ (for example if the area of the active part of the membrane is small compared to the cell membrane along the conduction pathway), then τ will be given approximately by

$$\tau \sim R_g\rho/R_\ell i. \tag{4}$$

Any of the terms on the right-hand side of Eq. 4 might represent a noisy variable, and thus be responsible for the variability of the ISIs. If either R_g or ρ is noisy, the distribution of ISIs will have the same form as the distribution of values of R_g or ρ.

[1] Assuming this current is charging the equivalent capacitance of the membrane, this criterion charge may be considered as a voltage level. In this sense, the integrate-and-fire model, as we employ it, is similar to voltage threshold models (e.g. Gerstein and Mandelbrot, 1964), except in the particular way in which the threshold is approached.

For mathematical convenience, we wish to consider variables distributed according to a normal distribution, a commonly found distribution in biological systems. The normal distribution is not a reasonable description of the distribution of ISIs, but an interesting result is obtained if either i or R_ℓ is the variable normally distributed. Since we are assuming i is constant, consider the case of a normal distribution of values of R_ℓ; that is the probability density function:

$$p_1(R_\ell) = [1/\sigma(2\pi)^{1/2}]\exp[-(\bar{x} - R_\ell)^2/2\sigma^2]. \tag{5}$$

The expected distribution of τ may be found from the relationship

$$p(\tau) = \left|\frac{dR_\ell}{d\tau}\right| p_1(R_\ell), \tag{6}$$

(Davenport and Root, 1958). Substitution in Eqs. 4 and 5 gives

$$p(\tau) = [R_g\rho/\sigma i\tau^2(2\pi)^{1/2}]\cdot\exp[-(\bar{x} - R_g\rho/i\tau)^2/2\sigma^2]. \tag{7}$$

We define two new variables:

$$\alpha \equiv i\bar{x}/R_g\rho, \tag{8}$$

and

$$\beta \equiv i\sigma/R_g\rho, \tag{9}$$

and consider only positive values of τ, so that Eq. 7 becomes

$$p(\tau) = [1/\beta\tau^2(2\pi)^{1/2}]\cdot\exp[-(\alpha - 1/\tau)^2/2\beta^2];\ \tau > 0 \tag{10a}$$

$$p(\tau) \equiv 0 \qquad ;\ \tau \leq 0 \tag{10b}$$

which we define as an hyperbolic normal distribution. This is the predicted ISI distribution for the simplest form of our model;[2] note that if we had not made the simplifying assumption that $R_g \gg R_\ell$, τ would be replaced by $(\tau - 1)$ in the argument of this equation, which would shift the density function one time unit to the right, increasing the mean by 1.0 while leaving the variance unchanged.

The ratio β/α determines both the shape of this distribution and the value of C; changes in α and β that keep this ratio constant are equivalent to a rescaling of τ, which is the same as a relabeling of the time axis. Thus the variables i, R_g, and ρ, which have no effect on this ratio, cannot affect C, although they do affect mean firing rate. The variables $\bar{x}$ and σ directly affect α and β, respectively, and therefore changes in either of these variables lead to changes in the value of C.

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[2]While it is true that the integral of Eq. 10*a* from $-\infty$ to $+\infty$ is unity, this equation does not give exactly the correct scaling for an ISI histogram, which is not defined for $\tau < 0$. When such values are discarded as physically unrealizable, the factor $1/(2\pi)^{1/2}$ must be increased such that $\int_0^\infty p'(\tau) = 1$; in fact, the correction is negligibly small if $\alpha > 2\beta$, as it is in many of the empirically derived fits to our data. In the figures, the amplitudes have been corrected by the appropriate factor.

The hyperbolic normal distribution will also be obtained from models in which either R_g or ρ is noisy if R_g or ρ is found to be inversely proportional to a normally distributed variable. In the case of R_g, this would mean that it is the conductance of the spike-generating mechanism that is normally distributed, a very reasonable possibility. In the case of ρ, it would mean the threshold is somehow determined by the quotient of some other variable that is normally distributed. We shall discuss the model as if R_ℓ were the noisy variable, but it should be understood that any of the four variables in Eq. 4 might equivalently be the noisy one.

We have so far assumed that a single common input current is shunted on its way to the spike-generating mechanism. However, it is reasonable to conjecture that there are several inputs to the spike-generating mechanism; one possibility is that inputs arriving along separate dendritic trunks might well be shunted independently. We have found (Levine and Shefner, 1975, 1977*a*) that the goldfish retinal ganglion cell receives inputs from at least four separate processes; these processes are responsible for the "on" and "off" responses from the center and surround mechanisms of the ganglion cell receptive field. These processes apparently interact with each other pre-emptively; that is, at any given time only one process determines the output, while the others temporarily have no effect. If two (or more) independent processes act so that at any time one of them pre-empts the others, some ISIs will be given by one and some by the other, and the distribution of ISIs will be a weighted sum of the distributions of ISIs due to each process. If the processes differ in their modal values, a multimodal distribution will result.

There is an implicit assumption in our model: the noisy variable takes values distributed according to a normal distribution, but it maintains a constant (or nearly constant) value for the duration of each ISI. The most direct mechanism would be one in which the variable takes a value and holds it until a spike occurs; the spike could serve as a trigger to reset the variable to a new (random) value. Such a formulation is assumed by Gestri (1971), in a model in which threshold (ρ) varies.

The other alternative is that the noisy variable changes its values independently of when the spikes occur. If the variable changes continuously but slowly, or if the intervals between changes are long compared to the ISIs, the model predicts the same results as when the variable resets at each spike, for it will be virtually constant within any given ISI. This formulation predicts high serial correlations between ISIs, with the serial correlations being greater and remaining large for higher orders when the firing rate increases. This prediction of high serial correlation coefficients is inconsistent with the data of Schellart (1973), although Gerstein and Mandelbrot (1964) noted some serial correlation, particularly for short intervals. If the relative rate of change of the noisy variable is taken to be of the same order as the ISI, the serial correlation coefficients become smaller (though the prediction of an increase with an increase in firing rate remains), but the predicted ISI distribution will be slightly different. As the rate of change greatly exceeds the rate of firing action potentials, the serial correlation coefficients should go to zero; however, the predicted distribution of ISIs becomes less

skewed, and the model no longer predicts that C will remain independent of firing rate. In the limit, this model approaches random-walk models and predicts an ISI histogram best fit by a gamma distribution of order equal to the ratio of the rate of change of the noisy variable over the firing rate.

METHODS

Data Collection

Experiments were performed on the isolated retinas of common goldfish (*Carassius auratus*), 15–20 cm long. Fish were stored in aquariums at about 25°C, with a light-dark cycle of 12 h each. Retinas were isolated by the standard procedure (MacNichol and Svaetichin, 1958; Levine and Abramov, 1975) and placed receptor side uppermost in an experimental moist chamber maintained at 24°C. Pure humid oxygen was directed at the retina at a flow rate of 90 ml/min.

Extracellular ganglion cell responses were recorded with etched platinum-iridium wire electrodes; the indifferent contact was made with a cotton wick soaked in the vitreous humor and looped around the edge of the retina. Action potentials were amplified, shaped into pulses by a level detector, and fed into a Hewlett-Packard 2100A laboratory minicomputer (Hewlett-Packard Co., Palo Alto, Calif.). The time of occurrence of each spike was recorded to the nearest millisecond; after each data collection period (or gate), the computer analyzed these data and printed a summary of the interspike interval statistics for that gate.

ISI histograms were accumulated in 50 bins of either 1, 2, or 5 ms for the 1st s of each gate (including the interval from the last spike in the 1st s to the first spike in the 2nd s); the bin width was selected to accommodate the firing pattern observed. These data were collected in conjunction with other experiments (Levine and Shefner, 1975, 1977*a*); after the collection of the ISI histograms (in darkness), various stimulus flashes were presented to the retina. However, there was at least 20 s of darkness preceding each second during which a histogram was accumulated. The histograms presented in this paper are the averages of 10–90 individual 1-s histograms, with at least 30 s intervening between consecutive gates. The rare 1-s periods in which fewer than five spikes occurred were discarded.

Curve-Fitting Procedures

Hyperbolic normal distributions were fit to the histograms obtained. Curve fitting was facilitated by noting that the histograms generally have a clearly identifiable mode. The mode, τ_m, of the hyperbolic normal distribution may be found by setting the first derivative of the probability density function to 0, giving

$$\tau_m = (1/2\beta)[(\alpha/2\beta)^2 + 2] - \alpha/2\beta^2. \tag{11}$$

We first determined the mode and chose an arbitrary value of β; α could then be calculated from

$$\alpha = 1/\tau_m - 2\beta^2\tau_m. \tag{12}$$

The amplitude of the predicted curve was then computed at τ_m and compared to the observed amplitude. An iterative procedure was employed to select a value of β for which these amplitudes matched. The complete predicted curve was then generated from the values of α and β.

Obviously, multimodal distributions cannot be fit by a single hyperbolic normal distribution. We have fit all our multimodal histograms with the weighted sum of two (or three) hyperbolic normal distributions, a scheme similar to that employed by Pernier and Gerin (1975) to fit bi-

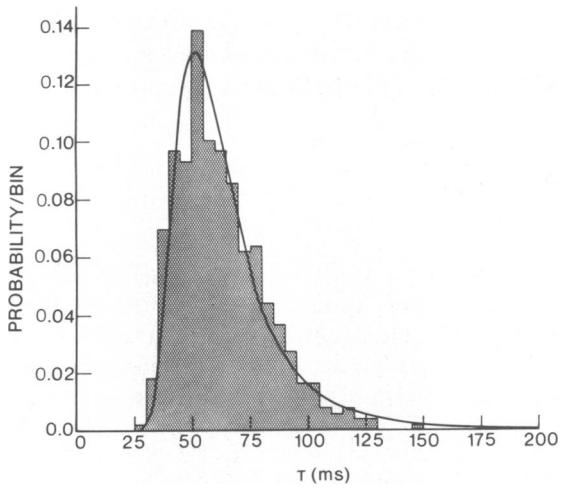

FIGURE 1 Distribution of 548 ISIs from a red off center ganglion cell firing at a rate of 16.12 spikes/s. The shaded area represents the histogram; the smooth curve is a hyperbolic normal distribution fit to the data ($\alpha = 0.0169, \beta = 0.0051$).

modal distributions. A weighting factor, a, was chosen that multiplied the first hyperbolic normal distribution; the second distribution was then multiplied by $(1 - a)$ so that the integral of the sum of the two density functions would be unity.

RESULTS

A total of 63 averaged ISI histograms were obtained from 36 different ganglion cells; of these, 16 cells were red "on" center units, 18 were red "off" center units, and 2 were apparently unresponsive. A typical unimodal histogram is shown in Fig. 1; the shaded area represents data and the smooth curve is a hyperbolic normal distribution. Most

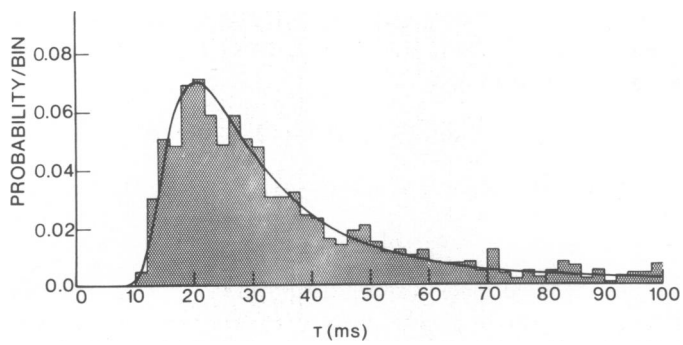

FIGURE 2 Distribution of 953 ISIs from a red off center ganglion cell firing at a rate of 24.57 spikes/s. The smooth curve is a hyperbolic normal distribution fit to the data ($\alpha = 0.0320$, $\beta = 0.0205$). (An additional 79 intervals were longer than 100 ms, and therefore do not appear on the figure.)

of the unimodal histograms obtained appear roughly similar to this one, displaying slightly more or slightly less skew. Some histograms, however, were highly skewed so that there was a finite probability of occurrence for intervals many times longer than τ_m. An example of such an histogram is shown in Fig. 2; a hyperbolic normal distribution has also been fit to this histogram. We did not observe any distributions approximating a Poisson distribution, in contrast to findings in the cat olivary complex (Goldberg et al., 1964), optic tract (Herz et al., 1964), midbrain (Škvařil et al., 1971), and forebrain (Smith and Smith, 1965). However, our observation is consistent with another study of goldfish isolated retina (Schellart, 1973), in which exponential distributions were found to be exceedingly rare.

Approximately half of the cells we observed displayed multimodal ISI histograms; generally two peaks were evident, though occasionally a third peak could be discerned. About 1/3 of the red on center cells and 2/3 of the red off center cells investigated displayed multimodal tendencies. Fig. 3 shows an example of a bimodal distribution in which the more prominent peak occurs at the shorter ISIs, Fig. 4 shows one in which the larger peak is at the longer ISIs, and Fig. 5 shows a trimodal histogram. During an experiment the same cell may exhibit each of the patterns exemplified in Fig. 3 and 4; that is, the relative magnitudes of the two peaks may change over time. In some cases the shift may be so extreme that a unimodal cell becomes bimodal, or vice versa.

DISCUSSION

The hyperbolic normal distribution predicted by our model gives qualitatively good fits to all the unimodal distributions we have obtained, using only two parameters. Similarly, the multimodal histograms can be fit by a weighted sum of hyperbolic normal distributions (five parameters for bimodal, eight for trimodal). The summation of

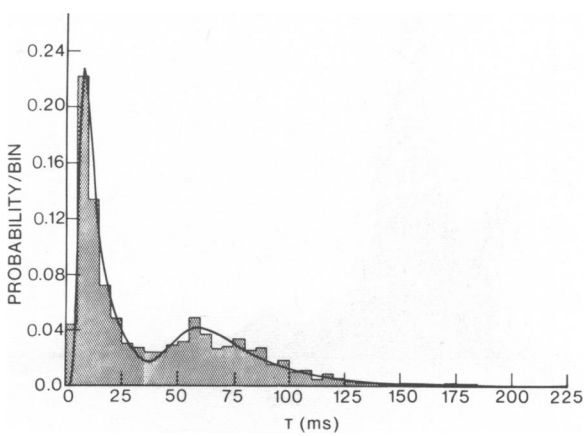

FIGURE 3 Distribution of 1,216 ISIs from a red off center ganglion cell firing at a rate of 26.44 spikes/s. The smooth curve is the weighted sum of two hyperbolic normal distributions fit to the data. One hyperbolic normal (α = 0.0595, β = 0.0640) accounts for 65% of the ISIs; the second (α = 0.0141, β = 0.0046) accounts for the remaining 35%.

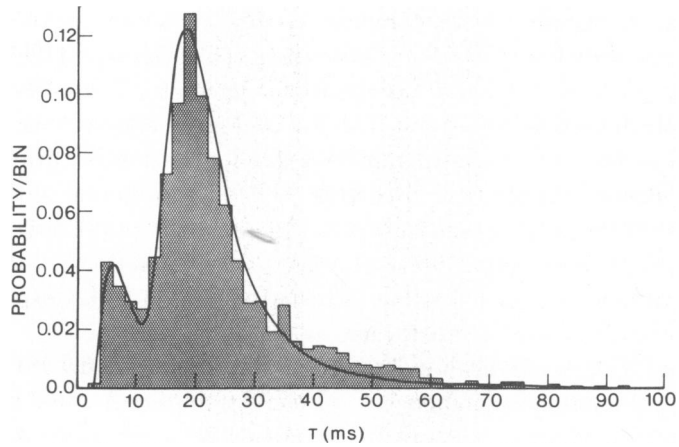

FIGURE 4 Distribution of 1,525 ISIs from a red off center ganglion cell firing at a rate of 43.60 spikes/s. The smooth curve is the weighted sum of two hyperbolic normal distributions fit to the data. One hyperbolic normal (α = 0.0960, β = 0.0770) accounts for 20% of the ISIs, the second (α = 0.0468, β = 0.0140) accounts for the remaining 80%. (One additional interval was longer than 100 ms.)

hyperbolic normal distributions to generate multimodal distributions is what is predicted if independent inputs pre-empt control of the spike-generating mechanism. We do not know what these independent inputs may be; however, possible candidates are the independent processes we have described for goldfish ganglion cells (Levine and Shefner, 1975; 1977*a*).

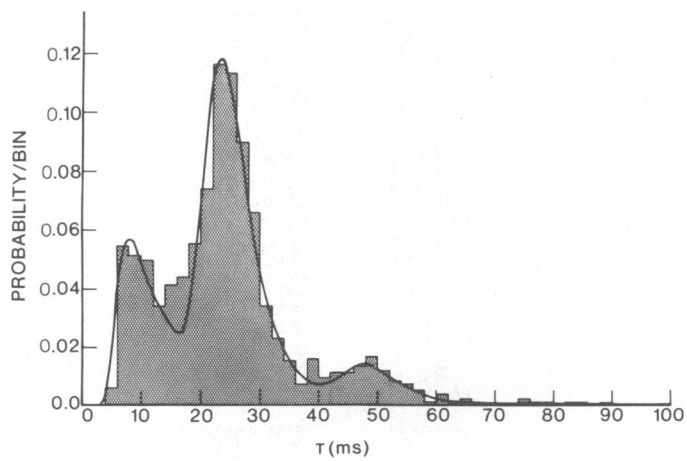

FIGURE 5 Distribution of 1,931 ISIs from a red on center ganglion cell firing at a rate of 41.98 spikes/s. The smooth curve is the weighted sum of three hyperbolic normal distributions fit to the data. One hyperbolic normal (α = 0.0625, β = 0.0625) accounts for 39.5% of the ISIs, a second (α = 0.0404, β = 0.0068) accounts for 53.5%, and the third (α = 0.0204, β = 0.0020) accounts for the remaining 7%.

An alternative mechanism that predicts multimodal distributions is one in which the cell somehow changes from a "bursting" state to a "resting" state. This is the premise of the "pseudo-Markov" model of Ekholm and Hyvärinen (1970). Schellart (1973) has found that goldfish ganglion cells do not meet the conditions of a Markov model, but this is not a necessary feature. This premise is also consistent with the suggestions of Smith and Smith (1965) that a "Poisson shower" is switched on or off by a mechanism either intrinsic or extrinsic to the cell. In this class of models, one process acts to determine the activity of a second process; while this is certainly possible, we believe that our observation of trimodal histograms renders it less likely than a mechanism in which independent processes pre-empt each other.

Still another possibility has been suggested by Ten Hoopen (1966*a*) and Bishop et al. (1964), who postulate the existence of inhibitory impulses which, when they coincide with an excitatory impulse, cancel that impulse. However, this scheme should predict that the second mode will lie in the range from two to about two and a half times the fundamental τ_m, depending on the strength of serial dependency of the ISIs and the exact shape of the distribution. In most of our distinctly bimodal histograms the second mode is 5–20 times longer than the first, which renders this an unlikely explanation for our data.

While the hyperbolic normal distribution gives a creditable fit to all of our observed ISI histograms, the gamma distribution (e.g. Kuffler, et al., 1957; Stein, 1965; Ten Hoopen, 1966*b*) sometimes provides a better fit. However, the gamma distribution does not afford good fits to many ISI histograms; for example the data in Fig. 2 cannot be fit by a gamma distribution of any order. More significantly, a change in input to the neuron would affect firing rate through a change in the order of the gamma distribution, leading to a positive correlation between C and total numbers of spikes. Thus, the gamma distribution does not readily satisfy the constraints imposed by our data.

One of the most interesting models in the literature is one in which a membrane potential is assumed to rise to threshold according to a random walk with superimposed drift (Gerstein and Mandelbrot, 1964; Johannesma, 1968; Pernier, 1972; Pernier and Gerin, 1975). This model yields an expression for predicting the ISI histogram that bears a superficial resemblance to the hyperbolic normal distribution; however, the two parameters of the equation may be identified with the threshold of the spike-generating mechanism and the drift or diffusion rate (excitation of the cell), rather than being related to parameters of the statistical distribution of a noisy variable. C would be related to the product of the two variables, and thus may easily be held constant while the firing rate changes if the threshold decreases as the excitation increases. However, one would expect to change the firing rate by changing excitation only; additional assumptions are needed for this model to satisfy the requirement of our data that C not be correlated with firing rate.

Other ways have been proposed to account for the shape of ISI histograms. Several schemes incorporate temporal properties in the spike-generating mechanism of integrate-and-fire models; these include a deterministic but changing threshold (e.g.

Rodieck, 1967; Stein, 1965; Geisler and Goldberg, 1966), and a "leaky" (Stein et al., 1972) or "forgetful" (Knight, 1972) integrator. Both of these features have been incorporated into the model presented by Schellart (1973), who predicted variously shaped ISI distributions based on an assumed Gaussian noise added to the input. But this model cannot predict that C will remain constant as firing rate changes, even if it is modified so that the noise multiplies the input.

Our model does hold C constant and provides qualitatively good fits to the data; however, a stronger test would be to submit our predictions to a statistical analysis. Predicting ISIs according to an hyperbolic normal distribution is equivalent to predicting that the distribution of the reciprocals of the intervals (instantaneous frequency density) be normal. One way to test whether a distribution is a normal distribution is to examine the moments (particularly the first four) of the distribution. We performed this analysis for the 25 clearly unimodal distributions we obtained. The first moment (mean) of the frequency density distributions agreed reasonably well with the values of α obtained by fitting the hyperbolic normal distribution to the ISI histograms. Similarly, the second moment (variance) agreed quite closely with the values of β^2. However, the third and fourth moments were significantly larger than expected for normal distributions of the given variances.

The analysis of the moments of the frequency density distribution indicates that while the hyperbolic normal distribution may predict a major portion of the variance of the ISIs, it does not completely account for the variability of the ISIs. Other sources of variability not distributed according to the hyperbolic normal distribution may be present (see below); in addition, even an ISI distribution that appears unimodal might have a second mode, which either is too small to be clearly discerned or is camouflaged by close proximity to the recognized mode. We thus should not expect the frequency density distribution to pass statistical tests for normality, in terms of moments, probit analysis, or any other criterion.

We could improve the correspondence of the model to our data by introducing various additional parameters. One obvious possibility is to change the assumed shape of the distribution of the noisy variable; of course, with complete freedom in choosing the shape of the input distribution, any output can be generated. However, with only a few very reasonable assumptions concerning upper and lower limits of an otherwise normally distributed variable, all the requisite corrections may be effected.

Another possible adjustment to the model would be to postulate an additional source of independent Gaussian noise; a multiplicative combination of this noise source with the hyperbolic normal distribution would allow us to fit any of the observed ISI histograms while retaining C's independence of firing rate. This second noise source could be extrinsic to the ganglion cell; that is, it could represent a variability of the input. Slow variations of the input that change the mean firing rate from sample to sample will smear the averaged ISI histogram, and increase the variability of the observed ISIs. There could also be a fast component of variability in the input current, arising either from synaptic noise in the distal retina, or from the receptors themselves (Rodieck, 1967). If invertebrate preparations are a valid indicator

of receptor noise, stimulation would act to reduce C in the receptors (Dodge, et al. 1968; Ratliff et al., 1968), so C should decrease for the on response. Our data (Levine and Shefner, 1977*b*) in fact show a small but significant decrease in C during the stimulus, regardless of whether the particular unit responds with an increase or a decrease in firing rate; that the decrease in C is very slight may indicate that this source of noise is a minor contributor to the total variability. Additional sources of noise might be intrinsic to the ganglion cell, representing rapid variations in any of the parameters in Eq. 4, or slow variations in the parameters in the numerator. The concatenation of a distribution derived from any of these sources with the hyperbolic normal distribution can satisfactorily fit any of our data.

We have presented our model as a possible mechanism that correctly predicts the shape of ISI histograms from goldfish ganglion cells while meeting the constraint that C be independent of changes in firing rate. This model is not applicable to all neurons; while many neurons in various parts of the nervous system display ISI histograms similar to what we have observed (e.g. Corrigall and Sherebrin, 1976; Kozak and Reitboeck, 1974; Pernier and Gerin, 1975; Pfeiffer and Kiang, 1965), others, such as those neurons that yield Poisson-like ISI histograms (see above) do not. Similarly, some neurons seem to share with goldfish ganglion cells the feature that C is constant over a considerable range of maintained stimulation (e.g. Gestri et al., 1966; Mastebroek et al., 1977), while others do not (e.g. Goldberg et al., 1964; Werner and Mountcastle, 1963). It seems reasonable to us that neurons may possess several mechanisms that contribute to the variability of ISIs, and that any of these may be the dominant mechanism in different neurons. The hyperbolic normal distribution is predicted by one possible mechanism that we propose for consideration as a contributor to ISI variability.

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