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Bruce Knight

Scott E. Brodie

Lawrence Sirovich

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Treatment of nerve impulse data for comparison with theory

BRUCE W. KNIGHT*, SCOTT E. BRODIE*, AND LAWRENCE SIROVICH**†

*The Rockefeller University, New York, New York 10021; and †Brown University, Providence, Rhode Island 02912

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ABSTRACT A procedure is given for the comparison of nerve impulse data with model predictions. This method utilizes information in the nerve impulse train that is ignored by the post-stimulus-onset histogram and thereby gives an improved signal-to-noise ratio. Comparison of observed responses in the *Limulus* retina with predictions derived from a detailed model gives good agreement.

The theory of the dynamical response of nerve networks has now advanced to the point such that detailed comparison can be made, in some cases, between nerve-impulse data collected in the laboratory and the theoretical prediction of how a neural network should respond to a specified input. This note presents some mathematical tools that facilitate an accurate comparison between theory and experiment.

An example of the situation that is treated below is shown in Fig. 1. Fig. 1A shows neural response data as they are commonly presented, in terms of a "post-stimulus-onset histogram." The histogram was constructed from responses, to 128 replicate stimuli, of a neuron in the retinal network of the *Limulus* lateral eye. Fig. 1B shows the theoretical prediction that corresponds to Fig. 1A (1–3). The theoretical variable shown, which corresponds to the post-stimulus-onset histogram, is the "population firing rate" (4). We note that the noise level in the post-stimulus-onset histogram prevents a detailed comparison between theory and experiment.

Fig. 1C treats the same nerve-impulse raw data in a different way, and it shows far less contamination by noise. It represents the estimated "mean individual rate" of the neuron. The superior signal-to-noise quality of this laboratory variable is achieved by a data treatment that utilizes information which the post-stimulus-onset histogram ignores—namely, that the impulse train of the *Limulus* visual neuron is not much affected by chance fluctuations in impulse arrival times. (Such a neuron will be referred to below as "sure-firing.") Fig. 1D shows the theoretically predicted mean individual rate, the counterpart of Fig. 1C (3). The quality of Fig. 1C is such that a detailed comparison with theory (Fig. 1D) is feasible; the noise problem in Fig. 1A has been surmounted. We observe, however, that the theoretical variable in Fig. 1D, the mean individual rate, is different from the population firing rate of Fig. 1B. It is in fact a step removed from the primary theoretical analysis of the neural network dynamics, which proceeds in terms of the population firing rate. The derivation of the individual rate from the population rate will be presented below.

To summarize, after the firing times of the sure-firing neuron's response have been recorded in the laboratory, the time course of that neuron's activity may be expressed by its "mean individual firing rate." On the other hand, the quantitative modeling of the response of a real neural network is phrased more naturally in terms of a different measure of activity, the "population firing rate." In order that theory may be used to

predict the results of experiment, the convenient theoretical measure of activity must be transformed to the low-noise laboratory measure. That transformation, and the consequent quantitative comparison of theory with experiment, is the subject of this note.

MEASURES OF ACTIVITY

Neurons may be classified, according to their firing behavior, into two broad categories: "irregular-firing" neurons whose firing periods show chance fluctuations under the best controlled circumstances, and "sure-firing" neurons whose firing periods are little affected by chance. Very different procedures are appropriate for summarizing the response activity of neurons at the extremes of these two categories.

Population Rate. For an irregular-firing neuron, the effect of chance fluctuations upon the firing-time data necessitates numerous repetitions of the same stimulation conditions. The data are naturally displayed in terms of a post-stimulus-onset histogram—that is, the time after the stimulus onset is divided into intervals, or "bins," and the histogram plots a sequence of heights that show the number of impulses that fell within each bin. The area under the histogram may be normalized to the average number of impulses per run, so that the histogram's height indicates the expected behavior of the neuron, independent of the number of runs. For good time resolution, the histogram must have narrow bins, and this, in turn, demands numerous run repetitions to achieve statistical accuracy within each bin. The limit of the normalized histogram for very narrow bins but also for indefinitely good statistical precision within each bin is called the *population rate* for the neuron under study. If a nerve cell receives parallel synaptic input from a population of similar neurons, then its expected intracellular postsynaptic potential will be related directly to the population firing rate of a representative neuron in that presynaptic population (5, 6).

Mean Individual Rate. A sure-firing neuron yields far more information in a few runs, or even in a single run, than would be revealed by a post-stimulus-onset histogram of those few data with any choice of bin width. After a single run, a revealing estimate of the neuron's activity may be obtained by assigning, to each time t , a rate estimate that is simply the reciprocal of the duration of the inter-impulse interval in which t falls. (A graph of this activity estimate resembles a set of steps of varying height that may rise or descend at firing times.) If several runs are available, we may average their individual activity estimates to obtain a smoother mean individual rate. In a real experiment, in which data acquisition time is severely limited, a sure-firing neuron will yield a stable activity estimate by this method after a far smaller investment of experiment time than is necessary to obtain a respectable post-stimulus-onset histogram. When the population firing rate changes only slightly between two firing times, the mean individual firing rate gives an accurate portrayal of the population firing rate.

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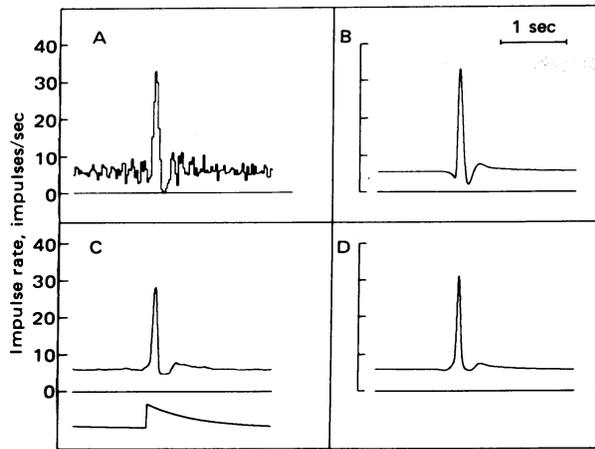


FIG. 1. Comparison of predicted and observed responses of *Limulus* retinal neuron to moving-step stimulus. (A) Observed post-stimulus-onset histogram (24-msec bin width). (B) Predicted population rate. (C) Observed mean individual rate response, and the stimulus light intensity pattern (below curve). (The records in A and C were computed from the same impulse train data, obtained in response to 128 presentations of the moving stimulus.) (D) Predicted mean individual rate response, obtained from B by means of algorithm described in the text. (Data from ref. 3.)

THEORY

In the circumstances of the laboratory (or of the creature in its natural environment), the activity level of a set of similar neurons may undergo a substantial change between the consecutive impulses of a typical member, and if this is the case there is no trivial relationship between the two measures of activity defined above. However, the mean individual unit rate may be derived from the population rate in a precise way.

The population firing rate, which we call $r(t)$, has been so defined that, for an ensemble of identical neurons, the fraction that fire in a short time, dt , will be given by

$$r(t)dt. \quad [1]$$

(The ensemble may be regarded as a very large number of repeated runs upon a single neuron or as a large set of independent neurons responding simultaneously to the same stimulus.) Between two times, t_1 and t_2 , the number of firings will equal the number of neurons in the ensemble if

$$\int_{t_1}^{t_2} dt r(t) = 1. \quad [2]$$

We now make the assumption that, if the identical neurons are sure-firing, between the firing times of a given member no other member of the ensemble will either fail to fire or fire more than once. (This assumption will hold for realistic causal impulse firing models, although unrealistic counterexamples can be contrived.) Thus, for a sure-firing neuron, Eq. 2 is the condition that if a neuron fires at time t_1 that same neuron will next fire at time t_2 .

Given that Eq. 2 relates the population rate to successive firing times, we may now relate the population rate to several variables that are relevant to the laboratory data-processing situation. The "instantaneous firing period" $\tau(t)$ (the time interval between a firing time t and the previous firing) is given implicitly by the relation

$$\int_{t-\tau(t)}^t dt' r(t') = 1. \quad [3]$$

Similarly, the "successor interval" $\theta(t)$ (the time interval from t to the next firing) is given implicitly by

$$\int_t^{t+\theta(t)} dt' r(t') = 1. \quad [4]$$

We now observe that, at time t , the mean individual rate $\sigma(t)$ will be the average of the instantaneous rate $1/\tau(t')$ over values of t' ranging from t to $t + \theta(t)$. This average is to be taken over each small interval dt' with a weight proportional to the number of firings within that interval—namely, with weight $r(t')dt'$. Thus, we have for the mean individual rate

$$\sigma(t) = \int_t^{t+\theta(t)} dt' \frac{r(t')}{\tau(t')}. \quad [5]$$

Eqs. 3, 4, and 5 furnish the transformation from the population rate to the mean individual rate. (This transformation is nonlinear because it does not satisfy the superposition property: If $r_1(t)$ yields $\sigma_1(t)$ and $r_2(t)$ yields $\sigma_2(t)$, the superposed population rate $r(t) = r_1(t) + r_2(t)$ does not in general yield $\sigma_1(t) + \sigma_2(t)$ as its mean instantaneous firing rate.

In practice, a numerical calculation based on a theoretical model for a neural network determines the population rate $r(t)$ on a mesh of discrete time points separated by a small time step dt . From this we may predict the mean individual rate $\sigma(t)$ as follows. Starting at time t , we sum $r(t')dt'$ backward in time until the sum exceeds unity and then interpolate to determine the fraction of the last step that yields the value of $\tau(t)$ that satisfies Eq. 3. We do this at each time step. Likewise we sum forward in time and similarly determine $\theta(t)$ in Eq. 4 at each time step. With $\tau(t')$ and $\theta(t')$ now on hand, $\sigma(t)$ may be evaluated from Eq. 5 by simple numerical integration.

The results of such a program are shown in Fig. 1. In this experiment (taken from ref. 3), a spatio-temporal transfer function for a *Limulus* ommatidium was empirically determined, in terms of the population rate r , by measurement of the response of this unit to sinusoidal grating stimuli flickering according to a sum-of-sinusoids signal (1). This empirical transfer function was then used to calibrate a Hartline-Ratliff model transfer function for use in theoretical calculations (2). We thus obtained the prediction for the response of this unit in terms of the population rate r (Fig. 1B). The depressions in the impulse rate that precede and follow the principal excitatory transient of the response reflect the inhibitory action of nearby ommatidia on the unit being monitored. These features are significantly attenuated, however, in the passage from the population rate to the mean individual rate (computed by means of the procedure described above), as shown in Fig. 1D. Nevertheless, this record agrees closely with the observed mean individual rate response (Fig. 1C).

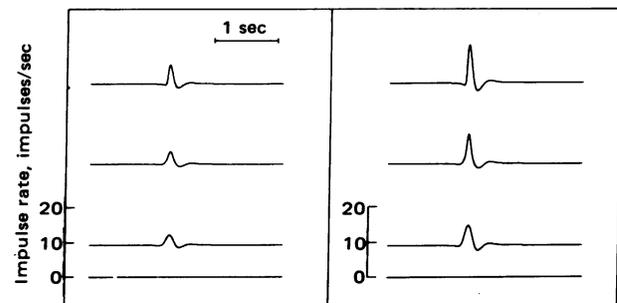


FIG. 2. Comparison of algorithms for conversion of population rate to mean individual rate. Top records: predicted population rate responses to low-contrast moving stimuli. Middle records: mean individual rate responses calculated from population rate by the exact nonlinear algorithm which is based on Eqs. 3, 4, and 5. Bottom records: mean individual rate responses calculated from population rate by means of linear transfer function of Eq. 10. Stimulus contrast for records at right is double that for records at left.

COMPARISON OF MEAN RATE AND HISTOGRAM PROCEDURES

It is natural to ask how the classical histogram procedure compares to the mean individual rate procedure, under real laboratory circumstances in which there is some stochastic variability in the impulse train. A comparison of the variances that the two procedures yield from a time-stationary impulse train should be indicative. In the nonstochastic limit of impulses generated by ticks of a clock, the individual rate gives zero variance. The variance of the histogram in that limit ranges from zero, if the binwidth (expressed in interpulse times) is an integer, up to a maximum of $1/4$ (expressed in terms of the square of the interpulse time), if the binwidth is an odd half-integer. An average of this variance over binwidths from $1/2$ to $3/2$ interpulse intervals gives an honest comparison with the other procedure. The equal-weighted average of the variance is $1/6$, a number stable to other sensible averaging methods. On the other hand, for entirely *uncorrelated* event times (Poisson occurrences) the variance of the individual rate is *infinite* while the same binwidth-average as above for the histogram variance yields unity. (All variances are expressed as multiples of squared mean interval.) Thus, our choice of procedure must depend on the degree of interpulse irregularity.

Both of the above extremes are limiting cases of the " Γ -renewal" process for which uncorrelated *intervals* are distributed with a probability density of the form $p_n(t) = (1/\tau)(t/\tau)^{n-1}/((n-1)!\exp(-t/\tau))$; $n = 1$ yields the Poisson case, and $n \rightarrow \infty$ yields the clock. For general n , the interpulse in-

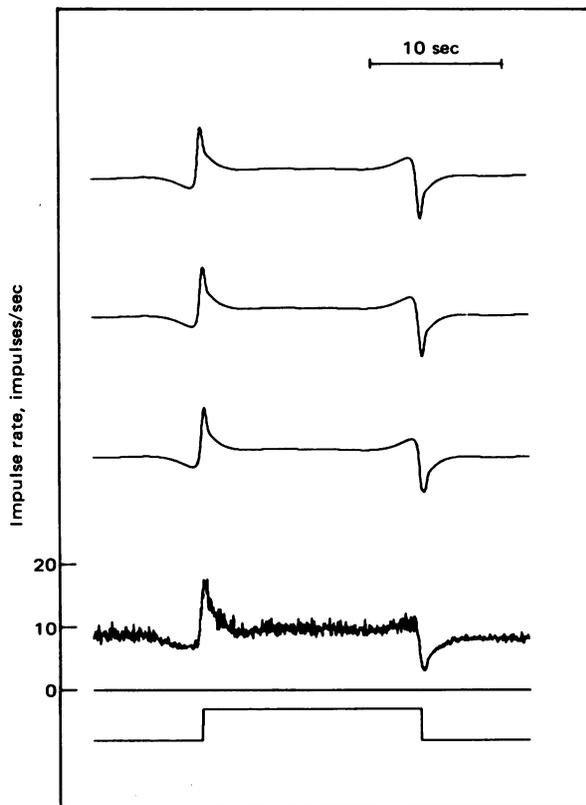


FIG. 3. Response to slowly moving stimulus. From top to bottom the records depict: predicted population rate response, predicted mean individual rate response calculated by the linear perturbation method, predicted mean individual rate response calculated by the full nonlinear procedure, and observed mean individual rate response obtained by averaging reciprocal inter-impulse data from 14 presentations of the stimulus. The light intensity pattern of the stimulus is shown at bottom. (Data from ref. 1.)

tervals have a coefficient of variation (standard deviation by mean) of $1/\sqrt{n}$. The variance of the individual rate is easily evaluated as $n^2/(n-1)^2(n-2)$. The variance of the histogram is far more elaborate; however, its binwidth average, asymptotic for large n , is $(1/6) + 1/n$, an expression that is within 8% of the exact result for $n = 2$, within 4% for $n = 3$, and $<1\%$ for $n \geq 5$. Hence, it may be used across the entire range of n . The ratio of the variances consequently is $R(n) = (n+6)(n-1)^2(n-2)/6n^3$. For $R(n) < 1$ the histogram procedure is more accurate. However, the inequality reverses and the individual rate procedure becomes the better when n exceeds about 6.25, which corresponds to an interpulse coefficient of variation of $1/\sqrt{6.25} = 1/2.5 = 0.4$; smaller coefficients of variation imply that the mean individual rate will furnish the more accurate result. For the *Limulus* eccentric cell, the coefficient of variation is about 0.1 (5, 7) which gives $n = 100$ and $R(100) = 17$. The implication is that, to achieve a post-stimulus onset histogram as accurate as the mean individual rate record with similar time resolution, under these circumstances one would have to collect the histogram data over 17 times as many runs.

PERTURBATION ANALYSIS

Under certain circumstances the population and mean individual rates may be more simply related. For example, if the population rate is a constant, r_0 , it follows that

$$\tau_0 = \theta_0 = \frac{1}{\sigma_0} = \frac{1}{r_0}. \quad [6]$$

More generally, we may consider small perturbations from the steady state. Specifically, we write

$$r(t) = r_0 + \epsilon r_1(t)$$

in which ϵ is small, $0 < \epsilon \ll 1$, and the ratio $r_1(t)/r_0$ is order unity. Under these conditions we seek a solution in perturbation form:

$$\tau(t; \epsilon) = \tau_0 + \epsilon \tau_1(t) + O(\epsilon^2)$$

$$\theta(t; \epsilon) = \theta_0 + \epsilon \theta_1(t) + O(\epsilon^2)$$

$$\sigma(t; \epsilon) = \sigma_0 + \epsilon \sigma_1(t) + O(\epsilon^2).$$

To obtain the $O(\epsilon)$ quantities θ_1 , τ_1 , σ_1 , we substitute these relations into Eqs. 3, 4, and 5 and expand in the powers of ϵ . To $O(1)$ we recover the steady relation 6, and to $O(\epsilon)$ we obtain

$$0 = r_0 \theta_1(t) + \int_t^{t+\theta_0} r_1(t') dt'$$

$$0 = r_0 \tau_1(t) + \int_{t-\tau_0}^t r_1(t') dt'$$

$$\sigma_1(t) = \theta_1(t) \frac{r_0}{\tau_0} + \int_t^{t+\theta_0} \left[\frac{r_1(t')}{\tau_0} - \frac{r_0}{\tau_0^2} \tau_1(t') \right] dt'.$$

From the first of these we have

$$\theta_1(t) = -\frac{1}{r_0} \int_t^{t+\theta_0} r_1(t') dt' = -\frac{1}{r_0} \int_t^{t+\tau_0} r_1(t') dt'. \quad [7]$$

From the second we have

$$\tau_1(t) = -\frac{1}{r_0} \int_{t-\tau_0}^t r_1(t') dt'. \quad [8]$$

Finally, when these are substituted into the last relation, we obtain

$$\sigma_1(t) = \frac{1}{\tau_0^2} \int_t^{t+\tau_0} dt' \int_{t'-\tau_0}^{t'} dt'' r_1(t''). \quad [9]$$

Eq. 9 is the desired linear relationship between the mean individual rate, σ_1 , and the population rate, r_1 . This relationship

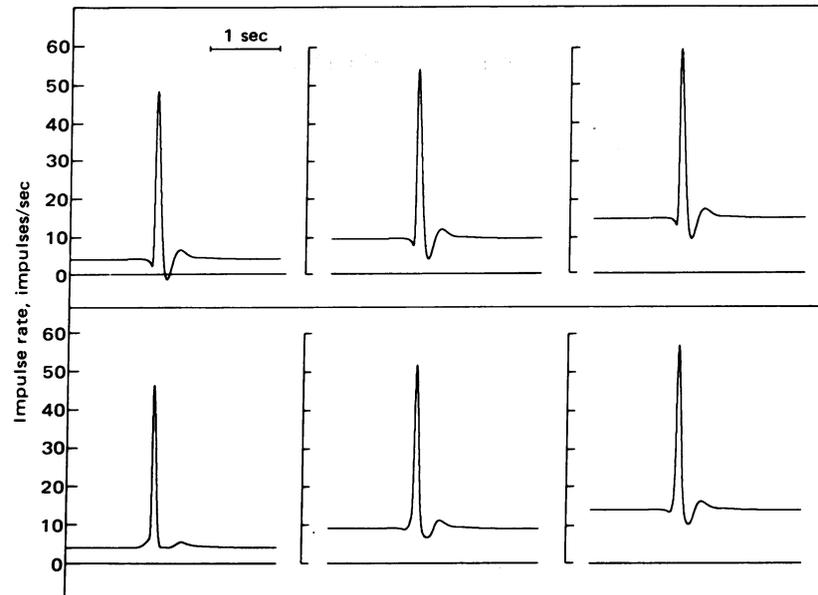


FIG. 4. Effect of mean impulse rate. (Upper) Predicted population rate responses to moving stimuli for hypothetical neurons with mean impulse rates of 5, 10, and 15 impulses per sec. (Lower) Corresponding mean individual rate responses.

also may be stated in terms of a transfer function. Thus, if the underlying stimulus is of the form $\exp(i\omega t)$, it follows that

$$r_1 = r_1(\omega)\exp(i\omega t),$$

$$\sigma_1 = \sigma_1(\omega)\exp(i\omega t).$$

Then, if these are substituted into Eq. 9, elementary integrations yield the transfer function

$$\frac{\sigma_1(\omega)}{r_1(\omega)} = \frac{2(1 - \cos\omega\tau_0)}{(\omega\tau_0)^2} = B\bar{B}, \quad [10]$$

which was also derived in ref. 1 by other methods. The form

$$B = \frac{1 - \exp(-i\omega\tau_0)}{i\omega\tau_0} \quad [11]$$

gives the transduction from the population rate to the "instantaneous frequency" of the neuron (4).

A theoretical example of the application of the perturbation analysis presented above is given in Fig. 2. The mean individual rate records at the bottom of the figure were obtained by computing the inverse Fourier transform of the product of transfer function 10 and the Fourier transform of the population rate. There is good agreement between the linear and nonlinear algorithms for stimuli of very low contrast. As the contrast is increased, the response can no longer be treated as a small perturbation, and the linear and nonlinear algorithms begin to produce divergent results.

The two algorithms (exact and linear approximations) for the conversion of the population rate to the mean individual rate also agree closely for the case of very slowly moving stimuli, as shown in Fig. 3. In this situation, there is essentially no difference between the population rate and the mean individual rate, and neither algorithm produces any significant alteration of the response record.

It is also of interest to note the effect of the mean impulse rate of the neuron under study on the transduction between population rate and mean individual rate (Fig. 4). Even for rapidly

moving stimuli and large contrast, the two output variables approach each other as the mean impulse rate increases.

In an experiment in which the population rate makes large departures from its mean value and substantial changes in the population rate occur between successive impulses of a single neuron, the full nonlinear algorithm given here is needed to make the conversion from population rate to mean individual rate, to compare theory with experiment. A sequence of experiments and comparison calculations, where this full treatment was necessary, will be published elsewhere (3).

In conclusion, a measure of neuron activity that we have called the mean individual rate can be estimated with much greater precision under common laboratory circumstances than can the population firing rate as estimated by classical post-stimulus-onset histogram. We have given an algorithm for the conversion of theoretical predictions from population rate to mean individual rate, and we have shown an example in which that conversion was both necessary and sufficient to give good agreement between theory and experiment.

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